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PharmGKB summary: mycophenolic acid pathway

Vishal Lamba^a, Katrin Sangkuhl^b, Kinjal Sanghavi^a, Alyssa Fish^a, Russ B. Altman^{b,c}, and Teri E. Klein^b

^aDepartment of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, Minneapolis, Minnesota

^bDepartment of Genetics, Stanford University, Stanford, California, USA

^cDepartment of Bioengineering, Stanford University Medical Center, Stanford University, Stanford, California, USA

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Introduction

Mycophenolic acid (MPA) is an immunosuppressive agent available either as an ester prodrug or as a sodium salt. Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester prodrug of MPA formulated to improve its bioavailability [1,2]. Mycophenolate sodium is a delayed-release formulation that delivers MPA to the small intestine without being released into the stomach. MPA is indicated as a prophylactic agent in patients receiving allogeneic renal, cardiac, or hepatic transplants. It is a noncompetitive, selective, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). IMPDH is an important rate-limiting enzyme involved in purine synthesis, which converts inosine monophosphate (IMP) to guanosine monophosphate (GMP) [3-5].

Pharmacokinetics

Following oral administration, the enteric-coated mycophenolate sodium is mainly absorbed in the small intestine where it is easily dissolved in the neutral pH of the intestine. The enteric-coated tablet thus has an advantage over the ester prodrug (MMF) in that it is less likely to cause gastric disturbances in patients [6,7]. The oral bioavailability of MPA after MMF administration ranges from 80.7 to 94% [8,9]. The mean elimination half-life of the drug is 9–17 h. In blood, up to 97% of MPA is albumin bound [8,10].

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Correspondence to Teri E. Klein, PhD, Department of Genetics, Stanford University Medical Center, Stanford University, 300 Pasteur Dr Lane L301, Mail Code 5120, Stanford, CA 94305-5120, USA, Tel: + 1 650 725 0659; fax: + 1 650 725 3863; feedback@pharmgkb.org.

Conflicts of interest

There are no conflicts of interest.

Orally administered MMF undergoes a rapid presystemic bioactivation to MPA by carboxylesterases (CES), mainly CES-1 and CES-2 [11,12]. A review by Bullingham *et al.* [9] reported that MMF was absent in plasma from healthy volunteers and renal transplant patients after its administration, which hints toward rapid conversion of MMF to MPA. Within the intestine, MMF is hydrolyzed to MPA, *N*-(2-carboxymethyl)-morpholine, *N*-(2-hydroxyethyl)-morpholine, and the *N*-oxide of *N*-(2-hydroxyethyl)-morpholine [11,12] by CES-2 (Fig. 1).

MMF that escapes initial intestinal hydrolysis enters into the liver through the portal vein and is converted to MPA in the hepatocytes. CES-1 and CES-2 are both expressed in the liver; however, only CES-2 is expressed in the intestine. The in-vitro hydrolysis rate of MMF is greater in human liver microsomes than it is in human intestinal microsomes [12].

Phase II glucuronidation of MPA is a major metabolic pathway mediated by intestinal and liver UDP glucuronosyl transferases (UGTs). Evaluation of heterologously expressed UGTs for MPA-7-O-glucuronidation in liver, kidney, and intestine microsomes demonstrated that MPA glucuronidation occurs primarily in the liver but also to some extent in the intestine and kidney [13]. The primary enzymes involved in MPA glucuronidation are UGT1A8 and UGT1A9, with minor roles for UGT1A1, 1A7, and 1A10. MPA-7-O-glucuronide (MPAG) is mainly excreted through urine by active tubular secretion and glomerular filtration. UGT1A8 and UGT1A10 are, however, expressed only extrahepatically and thus are responsible for MPA metabolism in the gastrointestinal tract [13-18]. UGT1A9 plays a predominant role in hepatic MPA metabolism [13,17].

Another metabolite of MPA is its acyl glucuronide form, Ac-MPAG (generated by UGT2B7), which has comparable potency to MPA [17,19-22]. Ac-MPAG induces cytokine release from mononuclear leukocytes, a likely cause of MMF side effects [23]. Ac-MPAG is a minor metabolite, and, although it works through the same inhibition mechanism as MPA, it was found to be a weaker inhibitor of rhIMPDH II as compared with MPA, suggesting that it would not be pharmacologically active and might not be contributing to MPA's effect [24].

The metabolite 6-O-desmethyl-MPA (DM-MPA) is formed by hepatic cytochrome P450 (CYP) enzymes, mainly CYP3A4 and CYP3A5, and to a lesser extent by CYP2C8 [25]. It undergoes further conjugation to form two glucuronides that constitute very minute fractions of MPA. Their structural identification was not possible, but they are theoretically assumed to be 4-O-phenyl and 6-O-phenyl glucuronides of DM-MPA [25].

MPAG and Ac-MPAG, and not MPA, are substrates for organic anion transporting polypeptides (OATPs). Using OATP-transfected human embryonic kidney (HEK) cells, it was observed that cells expressing OATP1B3 and OATP1B1 significantly accumulated MPAG [26-28]. MPAG and Ac-MPAG are excreted in the bile through canalicular multidrug resistance-associated protein 2 (MRP2) encoded by the gene *ABCC2*. Biliary excretion of MPAG is possibly also related to the observed gastrointestinal (GI) toxicity due to MPA. A study on Eisai hyperbilirubinemic rats (EHBRS), which were compromised in MRP2 because of the presence of mutations, showed rapid clearance of MPAG from plasma

but limited biliary excretion, suggesting its transport through MRP2 on the bile canalicular membrane [29]. The role of P-gp (MDR1) in oral absorption of MPA has been suggested by studies performed on MDR1a/1b (–/–) mice [30]. MPAG excreted in bile undergoes deglucuronidation by bacterial enzymes in the gastrointestinal tract to form MPA, which is again recycled [31]. Pharmacokinetic studies showed the appearance of a secondary peak of MPA after 6–12 h of oral administration, indicating enterohepatic circulation [31]. MPA is primarily excreted in urine as MPAG (87%) metabolite and in negligible amounts as MPA (< 1%) [4]. Using HEK293 cells for uptake experiments, Uwai *et al.* [32] suggested the involvement of human renal organic anion transporters hOAT3 (*SLC22A8*) and hOAT1 (*SLC22A6*). These results primarily supported the role of hOAT3 in cellular uptake and renal tubular secretion of MPAG. Another study using *Xenopus* oocytes also suggested the role of hOAT1 and hOAT3 in renal secretion of MPA and its metabolites [33]. As MRP2 is also expressed in the renal proximal tubule brush border membrane, it can potentially play a role in renal transport of MPAG.

Pharmacodynamics

Two major pathways of purine synthesis exist: the de-novo and salvage pathways. In the de-novo synthesis, which takes place in lymphocytes [3,34–36], the first step is the conversion of 5-ribose phosphate to 5-phosphoribosyl-1-pyrophosphate (PRPP). The next step is the incorporation of a purine ring on the ribose phosphate, which involves a series of reactions. These include conversion of PRPP to IMP. IMP is then dehydrogenated to xanthine monophosphate (XMP) by IMPDH and further to guanosine monophosphate by GMP synthase. GMP is converted to GTP and dGTP, which are involved in RNA and DNA synthesis, respectively. Conversion of IMP to XMP is the rate-limiting step in purine synthesis and is targeted by MPA (Fig. 1).

MPA has several mechanisms of action that are related. The basic mechanism of action of MPA is the selective inhibition of T-lymphocyte proliferation at the S-phase. This is carried out by selective inhibition of IMPDH, thus depleting the guanosine pool in the cell. Thymus and spleen lymphocytes have greater amounts of IMPDH, leading to greater cytostatic effect in these tissues as compared with other tissues [3,34]. Of the two IMPDH isoforms, IMPDH1 is expressed in most cell types, whereas IMPDH2 is expressed in activated lymphocytes [37]. MPA inhibits IMPDH2 up to four to five-fold more compared with IMPDH1, resulting in more potent cytostatic effects of MPA on lymphocytes than on other cells [3,35].

Furthermore, a reduction in GTP production decreases the expression of adhesion molecules that are responsible for recruiting monocytes and lymphocytes to the sites of inflammation and graft rejection [38]. Thus, the goal of MPA treatment is to reduce allograft rejection by acting as an immunosuppressant [3,5,34–36,39].

Pharmacogenomics

Genetic variants within the genes involved in MPA uptake and metabolism and in its targets have been reported to affect MPA pharmacokinetics and response in patients undergoing

transplantation. Some of the most significant studies reporting polymorphisms (SNPs) within *UGT1A9*, *UGT2B7*, *SLCO1B1*, *SLCO1B3*, and *IMPDH* are summarized below.

Genes encoding MPA metabolizing enzymes

UGT1A9 polymorphisms—UGT1A9 is highly expressed in the liver and is the major enzyme involved in MPA glucuronidation to MPAG [22]. Evaluation of the genetic variation in both *UGT1A8* (*2 and *3) and *UGT1A9* (*2 and *3) on MPAG formation identified *UGT1A8**3 as having significantly altered glucuronidation. However, the role of *UGT1A8**3 in the gastrointestinal tract has been implicated, as UGT1A8 is extrahepatic [13,22]. *UGT1A9**3 was associated with lower clearance and could have potential influence on inter-individual variation in the metabolism of MPA. However, their clinical impact is limited, as both of these SNPs (*UGT1A8**3 and *UGT1A9**3) occur with a minimum allele frequency of less than 5%. In another in-vitro study on human liver microsomes, novel polymorphisms were identified within *UGT1A9* that demonstrated high inter-individual variability in UGT1A9 expression. Several SNPs in the *UGT1A9* promoter region were found to be significantly associated with UGT1A9 levels. These include –2152C > T (rs17868320) ($P = 0.0004$), –275T > A (rs6714486) ($P = 0.0006$), –440C > T (rs2741045)/–331T > C (rs2741046) ($P = 0.046$), and –665C > T ($P = 0.042$) [40]. Follow-up studies identified a significant impact of promoter SNPs (rs2741045/rs2741046) in *UGT1A9* on MPA pharmacokinetics in renal transplant patients [41]. The presence of these *UGT1A9* promoter variants was associated with greater MPA exposure; however, MPAG levels were shown to be associated with renal function [41]. *UGT1A9* promoter SNPs (–275T > A/–2152C > T; rs17868320/rs6714486) (both occur in LD) have been associated with low MPA exposure in renal allograft recipients [42] and in healthy volunteers [43]. In healthy volunteers, the presence of *UGT1A9**3 was associated with higher exposure of MPA and Ac-MAPG [43]. Pazik *et al.* [44] also reported that the presence of *UGT1A9* promoter SNPs (–2152T/–275A) was associated with increased risk of rejection in Polish kidney allograft recipients. Another study on 338 renal transplant patients further confirmed the association of –275T > A/–2152C > T with lower MPA exposure in patients receiving tacrolimus in addition to corticosteroids and MMF, as a part of the immunosuppressive therapy [45]. In addition, *UGT1A9**3 was associated with higher MPA exposure when MMF was given in combination with tacrolimus or cyclosporine [45]. These results were also confirmed in another study in stable renal transplant patients in which promoter SNPs –275T > A/–2152C > T were associated with lower MPA exposure, and the carriers of these SNPs had higher incidence of gastrointestinal side effects [46]. Although the promoter SNPs –275T > A and –2152C > T are not found in the Asian population, Zhang and colleagues reported that in Chinese renal transplant patients another promoter SNP *UGT1A9**1b (deletion of T at –118: dT_{9/10}; rs3832043), which has been shown to enhance glucuronidation both *in vitro* and *in vivo* [40,47], was associated with increased enterohepatic circulation of MPA [48]. Dose-adjusted AUC_{6–12}, which is indicative of enterohepatic circulation, was higher in patients carrying at least one allele without T deletion (–118dT_{10/10} and _{9/10}) as compared with patients with T deletion [48,49]. The overall role of *UGT1A9* promoter SNPs has been explored for association with MPA pharmacokinetics as well as with the risk of rejection, although the studies have demonstrated consistent results in transplant patients with respect

to pharmacokinetics of MPA. More prospective studies are required to establish the benefit of genotyping in predicting the risk of rejection to further improve MMF therapy.

UGT1A8 and UGT2B7 polymorphisms—Sequencing of the first exon on *UGT1A8* in 254 Caucasians and 41 African Americans identified eight nonsynonymous SNPs. Stable expression of these variants in embryonic kidney cell lines identified a potential impact of UGT1A8*3 (C277Y; rs17863762), *5 (G173A240), *7 (A231T), *8 (S43L; rs372427845), and *9 (N53G) proteins on the formation of MPAG and Ac-MPAG, indicating the importance of these amino acids in enzymatic activity [22]. For *UGT2B7* variants, the impact was minimal. In Japanese renal transplant patients, none of the variants of either *UGT1A8* or *UGT2B7* had an influence on MPA plasma concentration [50]. Gastrointestinal side effects are a major problem in patients receiving MPA therapy, and evaluation of the *UGT2B7* 802C > T variant showed association of this SNP with fewer side effects (as compared with the wild type) when measured on a Gastrointestinal Symptom Rating Scale (GSRS) ($P = 0.009$) [51]. In another study focused on investigating the role of SNPs within *UGT1A8*, *UGT1A9*, *UGT1A7*, *ABCC2*, and *UGT2B7* on gastrointestinal adverse events, it was observed that patients with the *UGT1A1**1/*1 genotype (noncarriers of the variant *UGT1A8**2 allele) had a higher risk of diarrhea as compared with carriers of the *UGT1A8**2 allele (with *UGT1A1**1/*2 or *2/*2 genotypes) [52]. Further, as patients receiving a combination of MMF with either tacrolimus or sirolimus had a higher risk for diarrhea as compared with patients receiving a combination with cyclosporine, analysis according to cotreatment with other immunosuppressive agents showed significant association of *UGT1A8**2 with a higher risk for diarrhea in patients receiving MMF with cyclosporine [52].

Genes encoding transporters

SLCO1B1 and SLCO1B3 polymorphisms—*SLCOs* are the genes that encode for Organic Anion Transporter Polypeptides (OATPs). *SLCO1B1* and *SLCO1B3* are the genes implicated in uptake of MPA and its glucuronide metabolite MPAG into hepatocytes. Picard *et al.* [28] evaluated the role of OATP1A2, OATP1B1, and OATP1B3 in MPA and MPAG uptake using HEK cells and reported that cells expressing OATP1B3 and OATP1B1 accumulated more MPAG. Further, they observed a significant association of *SLCO1B3* SNP 334T > G/699G > A with MPA and MPAG pharmacokinetics in renal transplant patients receiving tacrolimus or sirolimus in combination with MMF but not in patients receiving cyclosporine in combination with MMF [28]. However, in a limited number of healthy Chinese individuals ($n = 42$) dose-adjusted MPA AUC_{4–12} was lower in adults carrying the *SLCO1B3* 334T allele as compared with those with the 334G allele; a similar association was not found in renal transplant patients coadministered prednisone. Two of the important covariates associated with MPA and MPAG levels in this study were weight and concomitant steroid use, indicating that these covariates should not be ignored when screening for genetic associations [53]. In contrast to the previous study, results from Japanese renal transplant patients demonstrated significant association of the *SLCO1B3* 334GG genotype with higher MPAG AUC_{0–12} as compared with the 334T genotype ($P = 0.027$). This implies that the ratio of MPAG/MPA levels was higher in GG homozygotes as compared with TT homozygotes, which is in accordance with the report by Picard *et al.*

[28]. With respect to OATP1B1 there are limited reports on polymorphisms, with one study by Miura *et al.* [27] showing higher dose-adjusted MPAG exposure in *SLCO1B1**1/*1 carriers as compared with carriers with the *SLCO1B1**15 allele ($P = 0.002$) and another study by Michelon *et al.* [26] reporting reduced MPA transport associated with the *SLCO1B1**5 allele ($P < 0.002$).

ABCC2 polymorphisms—MPAG is excreted in the bile primarily by MRP2 (*ABCC2*), and this transport is essential for enterohepatic circulation. Naesens *et al.* [54] evaluated seven SNPs in *ABCC2* for impact on MPA PK and observed that promoter SNPs rs717620 ($-24C > T$) and rs3740066 ($-3972C > T$) protect renal transplant recipients from a decrease in MPA exposure that is associated with liver dysfunction. In addition, they observed that $-24C > T$ SNP was associated with lower MPA clearance at steady-state conditions. All patients in this study received tacrolimus and corticosteroid in combination with MPA [54]. In contrast to the results mentioned above, among Chinese renal transplant recipients, *ABCC2*- $24C > T$ was not significantly associated with MPA, MPAG, or Ac-MPAG exposure levels. These patients received cyclosporine, which was speculated to have masked the effect of SNP [48]. However, another SNP, *ABCC2* 1249G $> A$, was found to be associated with higher Ac-MPAG levels as compared with wild type ($P = 0.016$) [48]. The combined effect of polymorphisms in *SLCO1B3* and *ABCC2* was reported by Miura *et al.* [27], where the clearance of MPA in recipients with both the *SLCO1B3* 334T $> G$ and *ABCC2*- $24C > T$ variant genotypes (334GG and $-24TT$) was significantly lower than in those with both the *SLCO1B3* (334T $> G$) TT and *ABCC2* ($-24C > T$) CC genotypes. Although the results indicated above showed possible interaction of genotype with the combination drug given along with MPA, a recent report suggested that MRP2-mediated transport of MPA is not influenced by cyclosporine, tacrolimus, or sirolimus [55].

Genes encoding the drug target

IMPDH polymorphisms—IMPDH1 and IMPDH2 are the targets of MPA and are responsible for the suppression of lymphocyte proliferation. Influence of IMPDH activity on MPA response has been reported by several studies (reviewed by Glander *et al.* [56]). SNPs in these genes might affect the immunosuppressive response, efficacy of MPA, and therefore acute rejection in transplant patients. However, the reports of association of SNPs with response and toxicity are not consistent and differ among studies. Evaluation of eight *IMPDH2* SNPs in de-novo kidney transplant patients identified only one intronic SNP, 3757T $> C$ (rs11706052), and the variant allele (C) was found to be associated with increased IMPDH activity ($P = 0.04$) [57]. In another study, an association was found between rs11706052 SNP and reduced antiproliferative activity of the MPA but not with any increase in the IMPDH activity [58]. In a study conducted on a cohort of Polish renal transplant patients, it was observed that *IMPDH2* rs11706052 was associated with a higher lymphocyte count ($P = 0.04$ at week 4 and $P = 0.068$ at week 8) and also with decreased lymphopenia ($P = 0.032$) in kidney allograft recipients; however, no association was observed with acute rejection, neutropenia, or GI disturbance [59].

With respect to *IMPDH1*, two intronic SNPs – rs2278293 and rs2278294 – have been shown to be significantly associated with the incidence of biopsy-proven acute rejection in the first

year after transplantation [60]. In renal transplant patients ($n = 456$), *IMPDH1* – rs2278294 SNP – was significantly associated with a lower risk of rejection and a higher risk for leukopenia during the first year after transplantation [61]. In Japanese renal transplant patients, *IMPDH1* variants – rs2278293 and rs2278294 – were associated with the development of subclinical acute rejection (which was dependent on night-time or daytime high MPA exposure), thus warranting further evaluation of these SNPs along with therapeutic monitoring of MPA in transplant patients [62]. The study focused on evaluation of phased haplotypes inferred from five *IMPDH1* SNPs (rs2288553, rs2288549, rs2278293, rs2278294, and rs2228075) and showed that carriers of the most common haplotype experienced GI intolerance as compared with noncarriers in pediatric heart transplant patients [63].

Cao *et al.* [64] studied the effects of *IMPDH* polymorphisms on 240 hematopoietic stem cell transplant patients and reported that, for the rs2278294 genetic variation, recipients with the GG genotype had a significantly higher incidence of acute graft-versus-host disease compared with recipients with the GA or AA genotype ($P = 0.002$).

Overall, SNPs in *IMPDH1* and *IMPDH2* have shown some significant association with MPA pharmacokinetics and pharmacodynamics, but the limited reports with inconsistent evaluation warrant a systematic evaluation of variants in these genes in a bigger cohort of patients.

Conclusion

MPA is an immunosuppressant used to prevent rejection in organ transplantation. Interindividual variability in the MPA exposure levels within and among populations has been observed. One of the reasons for this variability could be the interindividual variability in MPA pharmacokinetics and pharmacodynamics. MPA is extensively metabolized by several hepatic as well as extrahepatic UGTs and is a substrate for several influx and efflux transporters. Thus, SNPs within the key genes involved in MPA pharmacokinetics (*UGTs*, *SLCO1B1s*, *ABCC2*, etc.) and pharmacodynamics (*IMPDHs*) could have an impact on the MPA drug exposure and outcome. Here, we summarize studies reporting the clinical association of genetic variants in these genes with MPA exposure and risk of rejection or GI toxicity (one of the major toxicities associated with MPA). Further, as MPA is given in combination with other immunosuppressants such as tacrolimus or cyclosporine, impact of the combination drug used, or use of steroids, has been shown to influence the association with SNPs. Thus, in conclusion, it is crucial to comprehend MPA PK/PD pathways and various polymorphisms within the enzymes involved as well as consider other covariates (combination drug, weight, etc.) to improve the therapeutic benefit of MPA.

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Fig. 1.

Stylized cells depicting the metabolism and mechanism of action of mycophenolic acid. A fully interactive version is available at PharmGKB (<http://www.pharmgkb.org/pathway/PA165964832>). ABCB1, ATP-binding cassette, subfamily B (MDR/TAP), member 1; ABCC2, ATP-binding cassette, subfamily C (CFTR/MRP), member 2; Ac-MPAG, acyl glucuronide MPA; CES1, carboxylesterase 1; CES2, carboxylesterase 2; DM-MPA, 6-O-desmethyl-MPA; GI, gastrointestinal; GMP, guanosine monophosphate; IMP, inosine monophosphate; IMPDH1, inosine monophosphate dehydrogenase1; IMPDH2, inosine monophosphate dehydrogenase2; MMF, mycophenolate mofetil; MPA, mycophenolic acid; MPAG, MPA-7-O-glucuronide; SLCO1B1, solute carrier organic anion transporter family,

member 1B1; SLCO1B3, solute carrier organic anion transporter family, member 1B3;
XMP, xanthine monophosphate.