Pharmacokinetic-based Dosing Individualization of Mycophenolate Mofetil in Solid Organ Transplanted Patients

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Abstract: Mycophenolate mofetil (MMF) is an immunosuppressant drug approved for prophylaxis of transplant rejection in patients undergoing solid organ transplantation and is further employed in management of various autoimmune disorders. MMF exhibits notable pharmacokinetic inter- and intraindividual variability necessitating tailored therapeutic approaches to achieve optimal therapeutic outcomes while mitigating risks of adverse effects. The objective of this review was to summarize factors that influence the pharmacokinetics of MMF and its active metabolite mycophenolic acid in order to deduce recommendations for personalized treatment strategies. Presumed predictors were analysed in relation to each of the four pharmacokinetic phases, providing tools and targets for MMF dosing optimization amenable to clinical implementation.

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Introduction

Mycophenolate mofetil (MMF), the 2-(4-morpholinyl)ethyl ester prodrug of mycophenolic acid (MPA), is widely used as an immunosuppressive drug for the prophylaxis of organ rejection in recipients of allogeneic kidney, heart, or liver transplants (in combination with other immunosuppressants). Many reports have also been published that describe off-label use of mycophenolate mofetil in a wide range of nontransplant conditions, particularly autoimmune disorders (e.g. rheumatoid arthritis, systemic lupus erythematosus, psoriasis, granulomatosis, uveitis, and inflammatory bowel disease) (Bergan et al., 2021). However, in this review, we focus on its approved indications.

MPA is a purine analog that exerts its immunosuppressive effects by noncompetitive and reversible inhibition of inosine monophosphate dehydrogenase (IMPHD), a key enzyme in the *de novo* pathway of purine biosynthesis, which is essential for DNA replication during cell proliferation. MPA thus specifically blocks the proliferation and clonal expansion of T and B lymphocytes, providing an immunosuppressive effect (Monchaud and Marquet, 2009; Bergan et al., 2021).

MMF belongs to class II substances according to the Biopharmaceutics Classification System and exhibits a strong pH-dependent solubility profile (Yu et al., 2002). Following oral administration, MMF is rapidly absorbed and hydrolyzed to MPA by carboxyesterases in the stomach, small intestine, blood, liver, and tissues (Monchaud and Marquet, 2009). Maximum MPA plasma concentrations occur generally within 1 hour after MMF administration (Zhang and Chow, 2017). The bioavailability of MPA after oral administration of MMF is 94.1% in healthy volunteers, and thus indicates almost complete absorption (Zhang and Chow, 2017). MPA is poorly distributed into cellular factions (<5%), but is highly bound (97–99%) to serum albumin (Monchaud and Marquet, 2009; Zhang and Chow, 2017). Median apparent volume of distribution ranged between 101.5 and 176.1 l in thoracic transplant patients (Ting et al., 2008). MPA is extensively metabolized by the uridine 5'-diphospho-glucuronosyltransferase (UGT) system in the liver, gastrointestinal tract, and kidneys forming inactive MPA 7-O-glucuronide (via UGT 1A9 and UGT 1A8), and pharmacologically active acyl – MPA glucuronide (via UGT 2B7) (Zhang and Chow, 2017; Bergan et al., 2021). MPA is excreted primarily in urine in the form of MPA 7-O-glucuronide (87%), while only negligible amounts of MPA (<1% of dose) are excreted unchanged (Zhang and Chow, 2017). MPA 7-O-glucuronide is also excreted into bile by multidrug resistance-associated protein 2 (MRP2), and undergoes enterohepatic circulation (Zhang and Chow, 2017; Bergan et al., 2021). This phenomenon results in a second MPA peak at 6–12 hours after administration. It has been reported that up to 40% of the AUC (area under the curve) may arise from enterohepatic circulation (Zhang and Chow, 2017). The median apparent clearance value ranged from 12.7 to 36 l/h in

thoracic organ transplant patients (Ting et al., 2008). The mean elimination half-life of MPA is reported to range between 8 and 16 hours (Bergan et al., 2021).

Such complex pharmacokinetics suggests high variability, which is confirmed by studies reporting variability in the MPA exposure of up to 82% (Bullingham et al., 1996). Given that MMF is part of treatment regimens playing a key role in graft survival in patients undergoing a plethora of types of transplantations, it is pivotal to ensure adequate and personalized dosing, inter- and intraindividual variability of MMF accounted for. The aim of our review is to gather current knowledge about factors affecting MPA pharmacokinetics which can be thereupon utilized for individualization of treatment with MMF.

Influences on absorption

MPA shows nonlinear absorption kinetics, with large inter- and intra-individual variability (de Winter et al., 2011). MMF is rapidly absorbed in the upper gastrointestinal tract due to its high solubility at low pH (Monchaud and Marquet, 2009). On the other hand, dissolution experiments with enteric-coated formulations of mycophenolate sodium have shown that because of the enteric coating, MPA is released to the greatest extent at pH 6.0–6.8. Therefore, the drug is released in the small intestine rather than the stomach resulting in an unpredictable and highly variable t_{max} of 1.5 to 6 hours (Bergan et al., 2021). Absorption is almost complete under physiological conditions; however, gastrointestinal disturbances may result in significantly reduced bioavailability as shown in allogeneic hematopoietic stem cell transplantation recipients (Jacobson et al., 2007). Selective bowel decontamination resulting in changes in the gut microbiota also reduced enterohepatic circulation and consequently MPA bioavailability (Schmidt et al., 2001). MPA exposure can be reduced by 90, 26, and 17% due to chelation by iron supplements (ferrous sulphate), sevelamer, and antacids, respectively, when used concomitantly (Bullingham et al., 1996; Morii et al., 2000; Pieper et al., 2004). Furthermore, cholestyramine can inhibit enterohepatic circulation of MPA and decrease its AUC by 39% (Bullingham et al., 1998). Since dissolution of MMF may be inadequate at elevated pH levels in upper gastrointestinal tract, co-medication with proton pump inhibitors may affect the bioavailability of MPA. However, studies on this issue provide inconsistent results (Bergan et al., 2021). A randomized cross-over study does not show clinically relevant drug-drug interaction between pantoprazole and MMP in renal transplant patients (Rissling et al., 2015). Although pantoprazole slightly affects some MMF pharmacokinetic parameters, it did not have impact on IMPHD activity. Food consumption can decrease MPA C_{max} by 25–40%; however, the overall exposure is similar to that in patients under fasted conditions (Bullingham et al., 1996).

Influences on distribution

Hypoalbuminemia will increase the free fraction of MPA, resulting in reduced exposure due to faster clearance as described in liver transplant patients (Jain et al., 2007). No further factors have been observed to influence the MPA distribution.

Influences on elimination

Age did not significantly affect the pharmacokinetics of MPA (Tang et al., 2017). Renal function and plasma albumin concentration correlate with MPA clearance (Andrews et al., 2015). Since MPA 7-O-glucuronide is eliminated via kidneys, it accumulates in patients with impaired renal function. As a result of the recirculation of MPA 7-O-glucuronide to MPA, the MPA clearance appears to decrease. On the other hand, if patients are co-treated with cyclosporine, the recirculation of MPA 7-O-glucuronide is inhibited and thus MPA exposure decreases (Hesselink et al., 2005). Moreover, the accumulated MPA 7-O-glucuronide can displace MPA from its binding sites. The increase of unbound MPA due to elevated MPA 7-O-glucuronide levels or low albumin concentrations results in higher MPA clearance (Andrews et al., 2015). Cystic fibrosis patients had significantly lower MPA and MPA 7-O-glucuronide exposure when compared to patients without this disease. Trough and peak MPA levels were also reduced, while apparent clearance was significantly higher in patients with cystic fibrosis (Stuckey et al., 2014).

Glucocorticoids may induce UGT activity and thus increase MPA clearance. Discontinuation of glucocorticoids thus leads to a decrease in MPA clearance by 19% during 12-months period after glucocorticoids discontinuation (Cattaneo et al., 2002). However, clinical relevance of this interaction has not been exactly quantified. The only recommendation is to monitor MPA therapy during glucocorticoid discontinuation. In contrast, some non-steroidal anti-inflammatory drugs (niflumic acid, flufenamic acid, mefenamic acid and diflunisal) showed *in vitro* inhibitory effect on glucuronidation of MPA (Vietri et al., 2000). Co-medication with isavuconazole demonstrated 26% decrease in MPA clearance, which was mirrored in AUC increases (Groll et al., 2017). Since co-treatment with azole antifungals is common in solid organ transplanted patients, this drug-drug interaction may be of clinical relevance. Broad-spectrum antibiotics may affect the intestinal glucuronidase activity, thus interrupting enterohepatic circulation. The median MPA trough concentration was reduced by half during co-medication with ciprofloxacin or amoxicillin/clavulanic acid, while co-treatment with norfloxacin and metronidazole led to a decrease in MPA exposure by a third (Benjanuwattra et al., 2020). Rifampin reduces MPA exposure by 17.5% and trough levels by 48.8%, while increasing MPA 7-O-glucuronide exposure by 34.4%. This observation can be attributed to the induction of UGTs by rifampin (Naesens et al., 2006).

In like manner, genetic variability in UGT genes may also alter MPA pharmacokinetics (Hronova et al., 2014). Variants –275T/A and –2152C/T in the promoter region of the *UGT 1A9* gene are associated with an increase in glucuronidation activity, and therefore with a reduced MPA exposure (Hronova et al., 2014). Additionally, 1399 C>T polymorphism in the *UGT 1A9* gene has been described to alter MPA pharmacokinetics; more precisely, MPA trough blood concentrations were significantly higher in TT carriers than in CT and CC carriers (Ciftci et al., 2018). The *UGT 2B7* genotype has also been shown to contribute to the interindividual variability of MPA pharmacokinetics. In pediatric renal transplant recipients, MPA clearance was significantly lower in *UGT 2B7* 802 CC carriers compared to *UGT 2B7* 802 CT and 802 TT genotypes (Zhao et al., 2010). Besides UGTs, impact of polymorphisms in MRP2 transporter gene on MPA disposition was also tested, but rendered inconsistent results (Hronova et al., 2014). The observed higher MPA exposure in Asian patients compared with Caucasian or African American patients can possibly be attributed to the prevalence of gene polymorphisms within ethnic subgroups (Andrews et al., 2015).

Pharmacokinetic/Pharmacodynamic targets

Since the pharmacokinetics of MMF is complex and somewhat erratic, with large intra- and inter-individual variability, routine therapeutic drug monitoring (TDM) and dose individualization would unequivocally be beneficial. According to a consensus report by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology, there is sufficient evidence to recommend dose adjustments to achieve target MPA concentrations (Bergan et al., 2021). Nevertheless, there are several obstacles to routine implementation of this tool. First of all, since MPA plasma AUC has been shown to be the most predictive of clinical outcomes and single-point (trough level) measurement is a relatively poor predictor of MPA exposure, sampling strategy combining 3 concentration measurements within the dosing interval is the recommended method for TDM of MMF (Bergan et al., 2021). Furthermore, a population pharmacokinetic model with good predictive performance used in Bayesian simulation is essential for successful dosage optimization (Sima et al., 2019). Conversely, the population pharmacokinetics of MPA is more difficult to describe and requires models more complex than other immunosuppressants (Bergan et al., 2021). A target MPA $AUC_{0–12h}$ of 30–60 mg×h/l is recommended in kidney transplant recipients treated with MMF in combination with calcineurin inhibitor, with or without glucocorticoids (Bergan et al., 2021). The same target is recommended for liver transplant recipients treated with MMF with tacrolimus without corticoids. The MPA trough level is recommended to be between 1 and 3.5 mg/l, but with a lower level of evidence (Bergan et al., 2021). In *de novo* heart transplantation patients treated with MMF, calcineurin inhibitor and corticoids, MPA $AUC_{0–12h}$

> 36 mg×h/l or trough level > 2 mg/l is recommended. On the other hand, in lung transplant recipients, no evidence-based target can be proposed (Bergan et al., 2021). In order to improve MMF therapy individualization, range of potential pharmacodynamic biomarkers (e.g., IMPDH activity and expression) has been investigated with promising results. However, none of these biomarkers has been widely implemented in daily practice, partly due to the assays being arduous and labour intensive. All things considered, continued search for novel tools to improve MPA dosage personalization is warranted (Bergan et al., 2021).

Recommendation for dosing individualization, Conclusion

An approved initial MMF dose is 1 g twice a day in adult kidney transplant recipients or 1.5 g twice a day in liver or thoracic transplant patients. However, using this fixed initial dose, only 76.2% of kidney recipients co-treated with tacrolimus achieve the target MPA exposure of 30–60 mg×h/l by day 3, while merely 51.2% of patients reach this target range during co-treatment with cyclosporine (Andrews et al., 2015). The recommendations for individualizing initial dose of MMF can be summarized as follows:

- No dosing algorithms have been found for MMF (Andrews et al., 2015).
- Based on the well-described drug interaction between MPA and cyclosporine, the initial MMF dose increase by 30–50% should be considered in cyclosporine co-treated patients compared to patients co-treated with tacrolimus (Andrews et al., 2015).
- Iron supplements, sevelamer, antacids, and cholestyramine should be administered several hours apart from MMF.
- Special caution should be taken in patients co-medicated with wide-broad antibiotics, azole antifungals and strong inducers or inhibitors of UGTs, but without a specific recommendation on dose adjustment.
- Although there is a rationale for MPA TDM, its implementation into the clinical routine is demanding owing to the laborious sampling strategy along with the complex pharmacokinetics surrounding MMF.

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