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Mycophenolates: The latest modern and potent immunosuppressive drugs in adult kidney transplantation: What we should know about them?

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Abstract

Introduced in 1995, mycophenolate mofetil (MMF) would become the most powerful antiproliferative agent in the field of organ transplantation, thereby supplanting azathioprine, the first antiproliferative agent introduced in the early 1960s. Its association with tacrolimus greatly improved kidney transplant (KT) prognosis by significantly reducing the incidence of posttransplant acute rejection. MMF is also reputed to be a safe medication, but the frequency of the gastrointestinal complications associated with it, even minor ones, has induced the marketing of a second molecule called enteric-coated mycophenolate sodium. This late form of mycophenolate was supposed to be better tolerated thanks to its pharmacokinetic properties but the studies did not show significant differences between the two molecules. Otherwise, the combination of MMF with tacrolimus has significantly increased the risk of infections, particularly viral, and of neoplasia. To reduce this risk and avoid any situation of under or overexposure while remaining effective, only a strict and long-term monitoring of MMF allows the maintenance of already established therapeutic targets within the predefined ranges. In KT, individualizing the prescription and targets of MMF according to immunologic risk, global immunosuppression, and posttransplant period, as for other immunosuppressants, is open to discussion and may be beneficial.

KEYWORDS

adult, drug monitoring, kidney transplantation, mycophenolate mofetil, mycophenolic acid

1 | INTRODUCTION

The first attempts at kidney transplants (KTs) performed in humans during the 1950s were marked by great success in surgical terms, but total failure in medical terms. This failure arose from the immediate rejection of the graft, explained by the phenomenon of tissue incompatibility, a concept not yet well defined or resolved at that time. It was not until December 23, 1954, when the Boston team performed the first KT between genetically identical twins that medical success was achieved in the short-, mid-,and long-term, thus highlighting the importance of tissue compatibility between donor and recipient. However, KT could not be limited to monozygotic twins, and the idea was thus born of inducing tolerance to the alloantigens at the origin of failure. The first means used involved the total radiation of the recipient's body with injection of the hematopoietic cells of the donor, a potent protocol soon abandoned because of the serious secondary complications and the high rate of failure. With inspiration from anticancer chemotherapies to induce immunologic tolerance, the drugs initially tried were 6-mercaptopurine and methotrexate, both molecules particularly toxic and ineffective. Then in 1960, it was shown in Boston that azathioprine (AZA), a new derivative of 6-mercaptorurine, provided better protection from

experimental rejection, while being less toxic, but the first uses of azathioprine in humans were disappointing.[1] It was only in 1963 that the pioneering studies of Murray et al, and Starzl et al, showed that AZA can prevent kidney graft rejection in humans and that combination therapy with a steroid improved the global outcome.[2,3] A great advance was thus achieved in the field of immunosuppression in organ transplantation and in KT particularly, since the surgical technique of KT was already solidly successful. Thus, KT would undergo great development during the AZA era. Other important immunosuppressive drugs would also make triumphant entries onto the scene of KT, such as calcineurin inhibitors (CNI) cyclosporine (CsA) in 1976, and tacrolimus in 1994.[4,5] In parallel, immunosuppressive induction treatments would be developed and associated with different maintenance immunosuppressive therapies contributing to overall improvement in the prognosis of KT. During these years of glory, the development of techniques for the identification of the major antigens of the tissue histocompatibility system (human leukocyte antigen, HLA) would also experience great success, thus allowing better understanding of immunologic phenomena and assessment of immunologic risk. However, due to the side effects of azathioprine, the first true immunosuppressant introduced in KT, and its relatively weak immunosuppressive effect, the need of a new immunosuppressive drug with reversible antiproliferative effects which are more potent on lymphocytes than on other cell types, and without hepatotoxicity, nephrotoxicity, mutagenicity, and other serious side effects, was increasingly important and indispensable. It was in 1995 that the long-awaited medication, considered the "miracle drug," arrived—mycophenolate mofetil (MMF) the prodrug of mycophenolic acid (MPA). MPA exerts its immunosuppressive actions by inhibiting a key enzyme in the metabolism of purine bases, and thereby the proliferation of activated lymphocytes.[6] Since its registration for the prevention of acute rejection in KT by the United States Food and Drug Administration (FDA) and European regulatory agencies in 1995, MMF has become a first-line drug in the field of solid organ transplantation. A few years after its approval by the FDA, mycophenolate had largely replaced AZA in most immunosuppressive regimens, considering that 79% of KT recipients in the US received mycophenolate at hospital discharge.[7] Three historical studies, so-called pivotal trials, have compared mycophenolate to regimens containing placebo or azathioprine and have shown a reduced incidence of acute rejection after KT from 40%-45% to 20%-25%.[8–10] The strong results obtained from these three studies were the basis for the registration of MMF for the prevention of acute rejection after KT and the rapid spread of its use in field of all types of KT. Mycophenolate would also become the "most popular medication" in organ transplantation, mainly due to its reputation as a relatively "safe" drug associated with little, or at least manageable, toxicity. There are two therapeutic forms of mycophenolic acid used in clinical transplantation: MMF (brand name CellCept, Roche Pharmaceuticals, Nutley, NJ, USA) and mycophenolate sodium (MPS [brand name Myfortic, Norvartis Pharmaceuticals, Nutley, NJ, USA]). Different immunosuppressive protocols have been developed over the last two decades to lighten immunosuppression in view of reducing the risks of infection and neoplasia in transplant recipients. All these regimens include protocols without induction, protocols without steroids and protocols without calcineurin inhibitors, but MMF is nearly always present, whatever the protocol used. In 2009, The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggested that mycophenolate be the first-line antiproliferative agent.[11] Does MMF deserve this reputation of safe and effective immunosuppressive agent? We might also suppose that the great benefit brought by MMF is largely due to its association with tacrolimus, while AZA was often associated with CsA. The aim of this literature review is to describe the mechanism of action, the pharmacokinetics, pharmacodynamics, pharmacogenetics, monitoring, toxicity, drug interactions, the current place of the generics, and the real contribution of mycophenolate in the field of KT.

1.1 | Mechanism of action of mycophenolates

Mycophenolate mofetil is the ester prodrug of MPA is the active metabolite of MMF.[12] The term of MPA is usually used for describing the pharmacokinetics and pharmacodynamics of the active product, while the term MMF is used by practitioners to indicate the medication. MMF, an antiproliferative agent, is used clinically as part of immunosuppressive therapy, mainly in solid organ transplantation, hematopoietic stem cell transplantation, and various inflammatory and autoimmune diseases. MPA is a potent, selective, uncompetitive, and reversible inhibitor inosine-5′-monophosphate dehydrogenase (IMPDH), a key enzyme involved in the novo synthesis of guanine nucleotides in lymphocytes.[13] Guanine nucleotides are involved as substrates, activators, and regulators in many important anabolic processes in the cell, including biosynthesis of ribonucleic acid (RNA), deoxyribonucleic acid (DNA), and protein and transmembrane signaling. Guanine nucleotides are strongly required for mitogen and antigen-initiated proliferative responses. IMPDH is the essential rate-limiting enzyme in de novo synthesis of guanine nucleotides and is accounted for by the expression of two enzymes, termed IMPDH type I and type II, which are the products of two distinct genes. MPA is a threefold to fourfold more potent inhibitor of IMPDH type 2 compared with IMPDH type 1.[14] IMPDH activity is relatively high in proliferating cells and tissues with rapidly dividing cell populations. Proliferating B and T lymphocytes are singularly

dependent on the de novo, as opposed to salvage, pathway for purine biosynthesis, whereas other cell types can utilize salvage pathways. Inhibitors of IMPDH, which catalyzes the rate-limiting step in the de novo synthesis of guanosine nucleotides, have been shown to have a strong immunosuppressive effect. It leads to depletion of guanine nucleotide pools and retards the proliferation of T and B lymphocytes, thereby dampening both cell and humoral mediated immunity.[15] Why target lymphocyte cells in organ transplantation? Because they have a key role in the two phases of rejection reaction, sensitization, and the effector response. It is the T cells of the recipient that recognize the donor's foreign antigens and result in a cascade of intracellular signals leading to the synthesis of proteins including cytokines such as interleukin-2 (IL-2). What follows is a proliferation lymphocyte and a combined involvement of the mechanisms of cellular cytotoxicity, humoral response, and delayed type hypersensitivity reaction resulting in the destruction and apoptosis of the graft cells. Research on MPA developed from observations made on the mechanisms of genetic enzyme deficiencies involved in the metabolic routes of purine bases. It has been well established since the 1970s that children with an adenosine deaminase (ADA) deficiency present a combined immunodeficiency involving T and B lymphocytes, while children with a deficiency of hypoxanthine-guanine phosphoribosyl transferase (HGPRTase) have a normal immune system. That shows that the salvage pathway of purines, catalyzed by HGPRTase is not important for the immune system, while de novo synthesis, catalyzed by ADA plays a major role in the immune system. Starting from this observation, the strategy for developing an immunosuppressive treatment was first to obtain a phenotype copy of an ADA deficiency. It was therefore, necessary to inhibit IMPDH, the enzyme that limits the level of synthesis of the guanidine nucleotides. MPA fermentation product of *Penicillium brevicompactum* and its main action is to inhibit the isoform of type II of IMPDH, expressed in activated T and B lymphocytes. Selective inhibition of cellular IMPDH activity with MPA results in a cessation of DNA synthesis and cell cycle arrest at the phase Growth 1-Synthesis (GI-S) boundary.[16,17] This inhibition of cell replication is dose and time dependent, and the direct consequence of a reduction in cellular guanine ribo- and deoxyribo-nucleotide pools, because exogenous guanosine is able to abrogate the inhibition by being converted to guanine and salvaged into the guanine nucleotide pool.[18,19] MPA thereby inhibits the proliferation of human T and B lymphocytes and even when MPA was added as late as 72 hours after initiation of the proliferative response.[6,20] This cytostatic effect is about fivefold more potent on lymphocytes than on fibroblasts and other cell types, as expected from inhibitory effects of MPA on the two isoforms of IMPDH. Each isoform of IMPDH, type 1 and type 2, consisting of 514 amino acids with 84% sequence identity and encoded by two distinct genes, located at two different chromosomes.[21,22] Type II IMPDH is the predominant IMPDH isoform and is specifically linked to a wide range of cancers and lymphocyte proliferation. In activated T and B lymphocytes, type II isoform of IMPDH is predominant, while lymphoblasts possess more of the type I isoenzyme.[23] It was thought that IMPDH type 1 enzymes were constitutively present in the cells and that IMPDH type 2 would appear after immune activation.[23,24] Hence, both isoforms of IMPDH are responsible for the proliferation of the lymphocytes after transplantation and therefore, both isoforms should be inhibited to decrease the proliferation of the lymphocytes and to prevent acute rejections of the graft.[25] Dayton et al concluded that both type 1 and type 2 IMPDH should be considered important targets for immunosuppressive therapy.[26] Other effects are observed with MMF: decrease of apoptotic cells in renal tubular epithelium, inhibition of both T-lymphocyte subsets and their penetration rates through endothelial cells, inhibition of primary humoral responses, elimination of T-cells responding to T-cell receptor activation, inhibition of the induction and function of nitric oxide synthases, inhibition of antibodies formation, inhibition of contact hypersensitivity, and decreased expression of glycoproteins and adhesion molecules responsible for recruiting monocytes and lymphocytes to sites of inflammation.[27–29] All this contributes to attenuating the antigenic stimulation and inducing a state of immunologic tolerance vis-à-vis alloantigens. Note that, unlike calcineurin inhibitors, MPA uses a different mechanism of action and does not inhibit the production of IL-2 or the expression of the IL-2 receptor, but inhibits T cell proliferation at a late stage after IL-2 production. Figure 1 reports the main mechanisms of action of MPA in the lymphocyte cell.

1.2 | Pharmacokinetics and pharmacodynamics of MMF and MPS

Mycophenolate mofetil is a morpholinoethyl ester of MPA, while MPA is the main active metabolite of MMF. MPA is metabolized in the liver, intestine, and kidney, by uridine diphosphate glucuronic acid transferase (UDG-UGT) as glucuronidation at the phenolic hydroxyl group to form the 7-*O*-glucuronide conjugate.[30,31] MPA generates two major metabolites: 7-O-MPA-glucuronide (MPAG or M-1) and acyl glucuronide (AcMPAG or M-2). At least 90% of MMF is excreted in urine as MPAG whereas AcMPAG yield accounts for a small part of MMF. MPAG is the major urinary excretion product of the drug.[32] The bioavailability of MMF is excellent and 90% of MMF is found as MPA in plasma. After oral or intravenous administration, MMF is rapidly and completely hydrolyzed in the upper digestive tract, specifically at the stomach level, to produce MPA. In KT recipients,

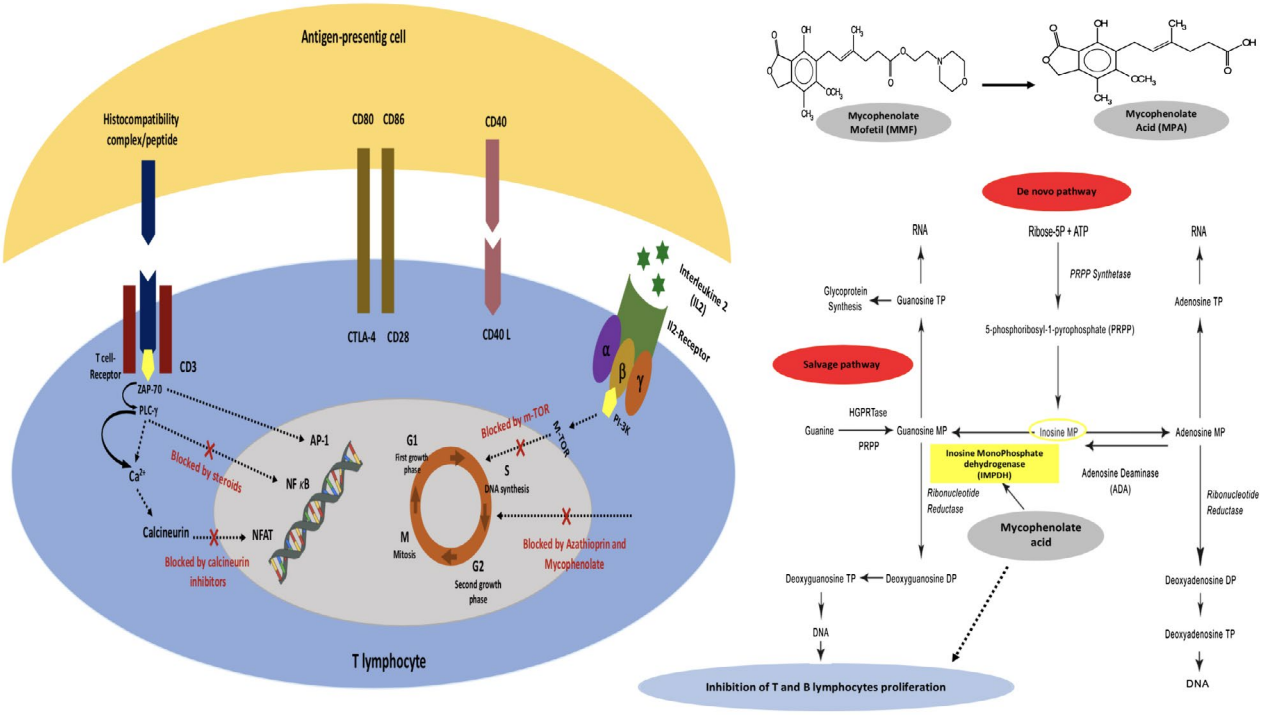

FIGURE 1 The main mechanisms of action of mycophenolate acid in the lymphocyte cell [Color figure can be viewed at wileyonlinelibrary.com]

no fraction MMF is measured at any time in plasma after its oral or intravenous administration.[33] Approximately 97 to 99% of MPA and 82% of MPAG are protein bound.[30] The pharmacokinetics of mycophenolate are complicated by the fact that there are many metabolites of MPA and they interfere with the active component, MPA. Both MPAG and MPA undergo enterohepatic recirculation, allowing sustained plasma concentrations of the drug, accounting for up to 10% to 60% of the total dose-interval MPA area under the concentration time curve.[30] Indeed, MPAG is transported from liver cells, where it is produced initially, into bile most likely via the ATP-binding cassette transporter MDR1-related protein 2.[34] Biliary MPAG then enters the gastrointestinal tract, where, under the catalytic action of glucuronidase that is shed from the intestinal flora, it is hydrolyzed back to MPA, which is then recycled into the bloodstream, the so-called enterohepatic circulation (EHC) pathway. The biliary excretion of MPA/MPAG and distal absorption involve several transport mechanisms, including the multidrug resistance-associated protein 2.[34] In pharmacokinetic studies, it was shown that the areas under the concentration-time curve for both M-1 and M-2 can account for 10% of those of MPA. M-2 can be present in predose and regularly observed in the plasma of liver, kidney, and heart transplant recipients undergoing treatment with MMF.[35] Some studies demonstrated that the M-1 shows immunosuppressive activity comparable to that of MPA.[35–37] However, AcMPAG is pharmacologically active against IMPDH type II isoform, but it is a weaker inhibitor than MPA and accumulated less in vitro in lymphocytes and therefore, is unlikely to contribute much to the immunosuppressant efficacy of MPA in organ transplant recipients in vivo.[35,38,39] So far it remains unclear whether these metabolites also contribute to adverse effects, even if recent studies showed that production levels of both metabolites M-1 and M-2 play a role in the adverse effects of MMF.[40] It should be noted that all the metabolites of MPA are excreted in urine, and any change of renal function can influence pharmacokinetics in a complex fashion, due to accumulated metabolite displacing MPA from albumin, effects of concomitant medication, and assessment of free, unbound clearance contrasted to total MPA clearance. In stable renal allograft recipients, MPA apparent clearance increased with glomerular filtration rate, and MPAG accumulated as renal function decreased, whereas in other literature reports, early after transplant, in patients with delayed graft function and/or severe renal impairment, total MPA exposure was low because of increased clearance due to increased free fraction of MPA.[41–43] MPS is another prodrug of MPA that was introduced into the clinical arena in 2002.[44] Its galenic presentation in the form of with enteric coating gastro-protected, extended-release tablets, i.e., with enteric coating (enteric-coated MPS, EC-MPS), was very advantageous and made its digestive tolerance more likely. MPS liberates MPA at a neutral pH into the small intestine, with the effect of slower absorption. Of note, is that the enteric coating of MPS results in maximal MPA concentrations that are achieved later in comparison with MMF. The typical concentration-time profiles of MPA reported in the literature presented a sharp initial peak around 1 hour and

smaller, secondary peaks at 6-12 hours postdose, attributed to enterohepatic cycling of MPA.[30,45] Regarding MPA pharmacokinetics and pharmacodynamics, it has been demonstrated that administration of nearly equimolar dosage of EC-MPS (720 mg) and MMF (1000 mg), results in a bioequivalent MPA full dose interval area under the curve (AUC), similar exposure to MPAG and AcMPAG and similar IMPDH inhibition.[46,47] Furthermore, in a controlled clinical study in de novo renal transplant patients, EC-MPS 720 mg twice a day has been shown to be therapeutically equivalent to MMF 1000 mg twice day.[44,48] The pharmacokinetics of MPA are characterized by a high between-subject and within-subject variability.[49] The main reasons explaining this wide variability are: differences in albumin concentrations, bilirubin and hemoglobin concentrations, impairment of renal and/or hepatic function, co-administration of cyclosporine, exposure to concomitant medication, body weight, time after transplantation, and gender and genetic polymorphisms in drug metabolizing enzymes.[50–52] The parallel use of therapeutic apheresis in a context of rejection or desensitization protocols in KT could expose the patient to an excessive elimination of mycophenolate. However, no study has compared plasma levels of mycophenolate in preapheresis, perapheresis, and postapheresis, and to date, there is no proof of elimination of mycophenolate. The guidelines on the Use of Therapeutic Apheresis in Clinical Practice of 2013 make no reference to this subject and specify only that patients should be started on immunosuppressive drugs prior to initiating therapeutic plasma exchange, to limit antibody resynthesis.[53]

1.3 | Pharmacogenetics of MMF and MPS

It is now well established that there is a pronounced interindividual variability in pharmacokinetics for the immunosuppressive drugs used in the areas of organ transplantation, such as cyclosporine, tacrolimus, MMF, and sirolimus and that polymorphism genetics can account for 20% to 95% of variability in drug disposition and effects.[54] Concerning MMF, several recent clinical investigations have shown that gene polymorphism is one of the important factors leading to MMF differences among individuals.[55,56] Thus, the individualization of medication regimens, based on different genotypes of patients, can contribute effectively to increasing the therapeutic efficacy and reducing the adverse effects of both forms of mycophenolate, MMF and MPS. Uridine diphosphate glucuronic acid transferase UGT1A8 plays an important role in the metabolism of MMF and MPS, producing respectively MPAG and AcMPAG. Clinical trials have shown that polymorphisms of the *UGT1A8* gene can affect MMF metabolism and that these polymorphisms are potentially related to MMF adverse effects. UGT participates in a variety of drug metabolism functions and is also one of the most important rate-limiting enzymes of MMF metabolism. These enzymes are broadly classified into twodistinct families, UGT1 and UGT2, which are further subdivided into three subgroups: UGT1A, UGT2A, and UGT2B.[57] *UGT1A8*, mainly expressed in the gastrointestinal tract and negligibly expressed in the liver, is mainly responsible for MPAG production, together with UGT1A9, and responsible for AcMPAG generation, together with UGT2B7.[58] Clinical studies have shown that *UGT1A8* gene polymorphisms not only affect the absorption and metabolism of MMF, but also have a certain potential relation with the adverse effects of MMF.[59] The authors of a recent study concluded, after ruling out several confounding factors such as patient influence and interaction with different associated drugs, that *UGT1A8* gene polymorphisms can affect MMF metabolism and that different single-nucleotide polymorphism (SNP) loci will lead to different activity of UGT enzymes.[60] Heterozygous Caucasian carriers of the UGT1A9*3 variant as a group were identified as a group that could benefit from a dosage reduction by about one-third, and data suggested that UGT1A9*1 carriers may need higher than average doses.[61] Another element that intervenes in the pharmacogenetics of MMF is the activity of IMPDH that also shows a large interpatient variability.[62] The sensitivity of MPA to inhibit IMPDH also differs between individuals, even when MPA levels are equal. The increased expression of IMPDH genes leads to increased IMPDH activity, and an increased IMPDH activity has been correlated with an increased cellular proliferation and transformation.[63]

1.4 | Therapeutic drug monitoring (TDM) of MMF and MPS

Theoretically, TDM of MPA seems evident and indispensable because it allows for regular verification of the efficacy of the prescribed dosage, the good tolerance and low toxicity of the drug. As for the other immunosuppressants (IS) used in KT, the therapeutic targets are situated within relatively narrow ranges, and any deviation from the target leads to potentially serious consequences. Below the targets, the risk of rejection with loss of the graft is high, and above the targets, toxicity, and secondary effects are frequent and may lead to serious complications that are life-threatening for transplanted patients. Usually, the prescribed doses of IS such as calcineurin inhibitors, are highly dependent on the body weight of the transplanted patient, while MMF is prescribed at fixed dose irrespective of patient weight. The usual prescribed dose of MMF is 2 g per day, this fixed dose seems high for adults whose body weight is under 50 kg and insufficient for adults whose body weight is over 80 kg. Note that for MMF, blood concentrations vary widely between individuals on fixed dosing (FD), due primarily to differences in the bioavailability

and clearance of MMF. If FD leaves an unacceptable proportion of individuals outside the range of safe and effective concentrations, then dosing to a therapeutic range, TDM, or a target concentration (target concentration intervention [TCI]) has the potential to both maximize the beneficial effect and minimize toxicities.[64,65] TDM is a traditional concept associated with empirical dose adjustment determined by a measurement being outside a "therapeutic range." Target concentration intervention (TCI) is a science-based method that uses pharmacokinetics and pharmacodynamics principles to identify how patients are different in terms of parameters such as clearance, volume of distribution, E_{max} (maximum effect), and C_{50} (concentration producing 50% of E_{max}), and gives the dose needed to reach the target. In this section we will discuss only TDM of MMF because only this method is well developed, validated, and recommended in KT, and it is due to its high degree of imprecision that TDM of MMF has always been subject to great controversy.[66] It is important to first remember all the monitoring strategies (MSs) that could be used in this area, and that all these strategies are based on the total MPA dosage. The first category of these MSs corresponds to two types of single measures, trough concentration (C_0, before dosing), and single concentration time (C_2, 2 hours after dosing or C_4, 4 hours after dosing) which are characterized by their simplicity in clinical practice, low cost, but also imprecision because they reflect plasma concentration at a given moment. The second category of these MSs corresponds to two types of multiple measures after dosing: multiple concentration time points (several specific timed points after dosing called Limited Sampling Strategies LLSs), an interesting and accurate tool but which requires multiple samples with increased risk of errors in estimation related to possible errors in timing; and single or multiple concentration time points, for Bayesian analysis. The third category of these MSs corresponds to full AUC ($AUC_{0\text{-}12\ hours}$, dose-interval AUC). In this third category, there are different methods for calculating full AUC. The most reliable consists of taking multiple blood samples spread over a period of 12 hours (more than eight samples for 12 hours) which allow a complete AUC to be obtained, but this is impracticable in clinical practice due to the excessive constraints on patients and personnel and its higher cost. To overcome this obstacle, mathematical formulas have been developed making it possible to calculate the AUC using a smaller number of samples and over a shorter period (2-5 samples for 4 hours). The use of linear regression algorithms has the major disadvantage of requiring strict respect of sampling times, while the Bayesian mathematical and statistical method allows calculation of the AUC based on three blood samples. Bayesian estimators have multiple advantages: they are more accurate than algorithms using multilinear regression models; they give estimates for all the patient's relevant pharmacokinetic parameters; and they estimate the complete AUC, allowing visual detection of slow or fast absorbers. They also are more adaptable to patients with unusual pharmacokinetics and are less sensitive to inaccuracies in sampling time. A Bayesian estimator has been designed using a limited sampling strategy (20 minutes, 1, 3 hours), with a bias of <10%.[67] Whether performed over 12 hours or a more limited period, the values obtained under 30 μg/h/L of MPA AUC are closely associated with acute rejection.[68,69] The large clinical trials comparing fixed doses to concentration-controlled doses based on MPA AUC measurements have given contradictory results. Two large, prospective, randomized trials have shown a relationship between early exposure and the risk for acute rejection in the first three postoperative months when conventional CNI-based regimens were used, although this relationship has not been shown for delayed rejections after 3 months posttransplantation.[70,71] The value of TDM of MMF lies in the fact that low MPA plasma concentrations have been found to correlate with a higher incidence of acute rejection after KT, especially in patients at higher risk of rejection.[72] It thus follows that rigorous monitoring reduces the incidence of posttransplant rejection and facilitates the appropriate adaptation of doses. Concerning the recommendations about TDM of MMF, since its introduction into the field of KT, they have been regularly discussed and research published from 1995 to 2010. The first recommendations published in 1995 did not suggest TDM of MMF, based on lack of interest in clinical practice.[45] In 1998, the consensus panel report suggested an MPA $AUC_{0\text{-}12\ hours}$ of 20 micrograms (μg)h/L or greater in adult renal transplant patients as a reasonable choice for the early posttransplant time period.[73] Later, in 2006, the conclusions of a roundtable meeting on TDM of MMF were published; they proposed a therapeutic window for MPA AUC of between 30 and 60 μg/h/L and suggested provisional target therapeutic ranges for MPA AUC and trough concentrations when using MMF in combination with either CsA or tacrolimus.[68] When combined with CsA, the recommended target ranges are 1 to 3.5 mg/L and 30 to 60 μg/h/L for trough concentrations and AUC, respectively. For the combination with tacrolimus, the target ranges of 1.9 to 4.0 mg/L and 30 to 60 μg/h/L for trough and AUC measurements, respectively, have been suggested.[68] Thus, MPA AUC remains the best predictor of acute rejection, hence the most relevant index of drug exposure.[74] In a recent in-depth review, the authors studied 27 cohorts including 3794 KTs, and found a significant relationship between MPA exposure and acute rejection in patients co-treated with tacrolimus as well as CsA.[64] The Randomized Concentration-Controlled Trial (RCCT) formed the basis for a target AUC between 30 and 60 μg/h/L.[75] This RCCT was conducted with 154 adult recipients of a primary or secondary cadaveric kidney graft who received MMF treatment aimed at three predefined target MPA AUC values (16.1, 32.2, and 60.6 μg/h/L) during the first 6 months after transplantation. The authors of

this RCCT showed that the incidences of biopsy-proven acute rejection in the low, intermediate, and high target MPA AUC groups were 14 of 51 (27.5%), 7 of 47 (14.9%), and 6 of 52 (11.5%), respectively, and the incidences of premature withdrawal from the study due to adverse events in the three groups were 4 of 51 (7.8%), 11 of 47 (23.4%), and 23 of 52 (44.2%), respectively. Four prospective, multicenter, randomized-controlled trials, the APOMYGRE (Adaptation de Posologie du Mycophénolate en Greffe Rénale), FDCC (The Fixed Dose–Concentration Controlled), OPTICEPT, and OPERA studies, have been performed in KT recipients, comparing concentration controlled (CC) TDM-guided, to fixed dose (FD) of MMF and achievement of fixed targets of TDM of MMF.[70,71,76,77] Results of these studies have been discordant. In the OPERA trial, the authors concluded that for the 80% of patients achieving therapeutic concentrations 3 weeks after transplantation, the MMF doses necessary to achieve therapeutic concentrations varied between individuals, suggesting that TDM should be used, but the rates of subclinical acute rejection at 3 months and 1 year were unexpectedly low, and not improved by TDM of MPA.[77] In the APOMYGRE study, 7 of 10 acute rejections occurring in the first 3 months posttransplant were associated with an AUC value less than 30 μg·h/L, 3 were associated with a value between 30 and 45 μg·h/L, and no episodes were seen in patients with an AUC greater than 45 μg/h/L, while in the recent CLEAR study (Cellcept Loading Dose in Early Posttransplant Period in Renal Allograft Recipient), kidney recipients receiving tacrolimus who exceeded an MPA AUC of 30 μg/h/L on day 5 have had much reduced acute rejection rates.[76,78] While the lower limit of the target (30 μg/h/L) seems quite well correlated with the relevant clinical data, that is not yet the case for the upper limit of the target, for which the role has yet to be-defined (60 μg/h/L). The frequency and rhythm of follow-up by AUC have not been specified, but all the recommendations agree about implementing follow-up by AUC in specific populations of KT recipients such as pediatric transplant patients, dual immunosuppressive therapy, reduced-dosage CNI therapy (including delayed introduction of CNI), CNI switch or withdrawal, recipients with high immunologic risk, delayed graft function (renal, hepatic, bowel), altered gastrointestinal/hepatic/renal function, Cystic fibrosis, Drug interactions, and noncompliance.[68] What about MPS? A dosage of 720 mg of MPS provides bioequivalence to a dosage of 1000 mg of MMF in KT patients and it would seem that the rules of TDM for MMF would also apply to MPS. However, this is definitely not true. Because of a more marked variability of its pharmacokinetic characteristics related to a less predictable, delayed, and prolonged absorption, it has not yet been possible to propose an AUC approach by linear regression algorithms or Bayesian estimators for MPS.[68] Several authors have experimented with the full AUC MPS, using both the measurements over 12 hours and the measurements over 4 hours in kidney recipients, but all of these measures are associated with a high failure rate because of its delayed absorption and result in biased and imprecise results.[79–81] In other studies, and despite the highly variable absorption data of MPS, an appropriate LSS might be estimated by MPA $AUC_{0\text{-}4\ hours}$ and IMPDH area under the enzyme activity curve (IMPDH $AEC_{0\text{-}4\ hours}$) in renal transplant patients treated with EC-MPS and CsA. According to these studies and regarding adverse events, the suggested MPA-target $AUC_{0\text{-}12\ hours}$ from 30 to 60 μg/h/L seems to be appropriate in renal allograft recipients.[82] Better and accurate measures may require the performance of a full 12-hour AUC to capture MPA exposure efficiently.[68] For patients who require MPA TDM, MMF is currently the most practical therapeutic option and EC-MPS might be best reserved for use in those KT recipients who do not require TDM. In other words, this medication is to be avoided in patients at high immunologic risk and therefore high risk of rejection. It is very important to be aware that most data concerning MPA TDM in the KT area is obtained in the short-term posttransplant, generally in the first 3 months posttransplant, and that very few data are available concerning MPA TDM in the long term, especially after the first year posttransplant.[75] In contrast, the studies done necessarily included variables with great impact on MPA TDM, such as the presence of rejection risk with recourse to strong immunosuppression, concurrent medications, concomitant immunosuppression, treatment of rejection, malnutrition and weight loss posttransplant, associated comorbidities, diet, and treatment adherence. It is also important to point out that the original target range of MPA (30-60 μg/h/L) was established in a study using CsA and steroids, while currently the majority of KT recipients are given tacrolimus instead of cyclosporine, as well as inhibitors of mammalian target of rapamycin.[8–10,83] Thus, further studies are also needed to establish whether this target is valid for other combinations of immunosuppression (e.g., tacrolimus or sirolimus/everolimus and/or steroid regimens). Figure 2 reports the therapeutic target of MPA and the risk of complications according to MPA monitoring values in KT recipients. Since its introduction on the market of KT in 1995, several recommendations have been published addressing the different aspects of MMF.[11,45,68,73,84–88] All these international guidelines concerning TDM of MMF are summarized in Table 1.

1.5 | Adverse effects, toxicity and drug-drug interactions of MPA

1.5.1 | Adverse effects and toxicity

The band molecule of MMF (Novo-Mycophenolate Teva Pharmaceuticals, CellCept Roche Pharmaceuticals) is available as 250 mg capsules and 500 mg tablets. MMF (Novo-Mycophenolate) capsules and tablets are contained in a blister

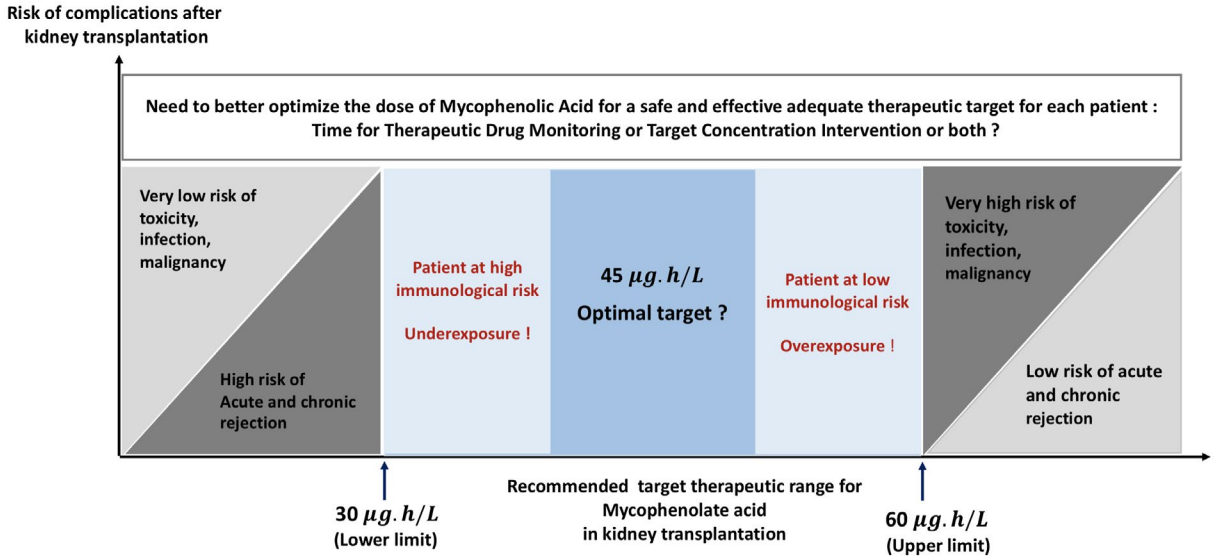

FIGURE 2 The therapeutic target of mycophenolate acid (MPA) and the risk of complications according to MPA monitoring values in kidney transplant recipients [Color figure can be viewed at wileyonlinelibrary.com]

pack, which should not be opened until the dose is to be administered. MPS (Myfortic Novartis Pharmaceuticals, Apo-Mycophenolic Acid, Apotex) is available in two strengths of enteric-coated tablets for oral use containing 180 mg mycophenolic acid as MPS and 360 mg mycophenolic acid as MPS. Tablets are provided in blister packs. The tablets are not be crushed or cut. Based on the experience accumulated during the first clinical trials, MMF is not toxic to the kidney, the liver or the central nervous system although gastrointestinal toxicity is greater in MMF patients than in control patients. To this point, there is no accurate obvious relation between drug exposure (MPA AUC) and MMF related toxicity, knowing that the incidence of adverse effects increases with increasing doses. Metz et al, in their recent review, analyzed 22 cohorts involving 3225 KT recipients and found a relationship between MPA $AUCt_{0\text{-}12\ hours}$ and hematological or infectious toxicities, and this relationship was more marked in patients co-treated with tacrolimus than with CsA.[64] Despite its "safe" reputation, MPA has been associated with several complications that can be stratified into four categories: gastrointestinal (GI), hematological, infections, and malignancies. This poor tolerability of mycophenolate due to emergence of adverse events in practice may require dose reduction, temporary interruption or permanent discontinuation. GI complications are one of the most frequent and important complications of MMF observed in KT patients. Among these GI complications we find mainly nausea, vomiting, heartburn, dyspepsia, anorexia, abdominal pain and especially diarrhea. The diarrhea is defined as more than three loose stools per day and it is the result of inflammation, infection or malabsorption among other causes. The incidence of diarrhea within the first year after KT reached 42% for a 2000 mg daily dose of MMF in patients using the combination of tacrolimus or CsA and MMF.[89] In this study, the prevalence of diarrhea was 22%, 29% and 42.3% ($P < .05$) in patients with tacrolimus + corticosteroids, tacrolimus + corticosteroids + MMF 1 g daily and tacrolimus + corticosteroids + MMF 2 g daily respectively. The authors of this study concluded that a higher dose of MMF (2 g daily) is associated with greater toxicity without a significant improvement in efficacy. It seems that both MPA and its metabolites may cause GI effects. However, no relation was demonstrated between diarrhea and the plasma concentration of the reactive acyl glucuronide metabolite of MPA.[90] The direct action of MPA is related to its antiproliferative properties by inhibiting the replication of GI epithelial cells that lead to disruption of fluid absorption and diarrhea. Villous atrophy in the duodenum and erosive inflammation in the ileum have been observed in patients with MMF-associated diarrhea.[91,92] Impairment of the global enterocyte function through either a higher apoptotic rate or an impaired function of the tight junctions leading to leak-flux diarrhea have also been observed. Sometimes the digestive disorder may take on the appearance of an inflammatory ulcerative ischemic colitis, "Crohn's-like enterocolitis associated with mycophenolic acid," which is a rare but potentially serious complication.[93–95] Nephrologists and gastroenterologists should be aware that patients treated with MMF who show ulcerative inflammation in the small bowel or colon may have drug-induced enterocolitis.[95] Thus, discontinuation of the MMF therapy is the approach of first choice, and may quickly lead to recovery, obviating the need for pharmacotherapy directed at Crohn's disease. The usual approach to serious diarrhea (more than four stools a day), is to first eliminate the other etiologies of diarrhea, especially infectious etiologies. If the diarrhea is related to taking MMF/MPS, it is recommended that for a short period, the medication should be taken with meals; dose splitting (twice daily to 3 or 4 times daily), and/or reduce the doses by 50%; temporarily stop the

TABLE 1 Summary of the main international guidelines concerning therapeutic drug monitoring (TDM) of mycophenolate mofetil (MMF) and mycophenolate sodium (MPS)

Recommendations	Target of MPA exposure	Indications of TDM of MMF
Mycophenolate mofetil: a report of the consensus panel (1995)	The optimal sampling time for MPA concentration measurement is under investigation. It is recommended that selection of an optimal sampling time be based on an analysis of AUC data collected during clinical trials for renal transplant patients. It is recommended that the analysis identify which single time point (e.g., 12 hours trough or C average) correlates best with MPA AUC and whether or not an abbreviated AUC provides better correlation than the single time point	Population with expected large variability in pharmacokinetics behavior in order to individualize MMF dosing: liver transplant patients early after transplantation; pediatric transplant; altered absorption (e.g., diarrhea), drug-drug interaction; dietary factors
Therapeutic monitoring of mycophenolic acid a consensus panel report (1998)	Evaluation of MPA AUC may be valuable in the following circumstances: To establish that adequate MPA concentrations are present early after transplant surgery. To provide a basis for how flexible the practitioner can be in dose reduction of MMF to avoid adverse reactions. A therapeutic window has not been established for MPA $AUC_{0\text{-}12}$ or single time point samples such as C_{max} or predose. An MPA $AUC_{0\text{-}12\ hours}$ of 20 μg/h/mL or greater in adult renal transplant patients is a reasonable choice for the early posttransplant time period	No data
Mycophenolate mofetil: suggested guidelines for use in kidney transplantation (2001)	The development of MMF as an immunosuppressant is still in its early stages. The dosage recommendations are preliminary. It seems irrational to give a drug like MMF in a fixed dosage for an indeterminate period from the day of transplantation. The preliminary data with therapeutic drug monitoring are promising and will help to expand our current knowledge on the use of MMF	No data
Report of the American Society of Transplantation conference on immunosuppressive drugs and the use of generic immunosuppressants (2003)	No data	No data
Therapeutic drug monitoring of mycophenolate mofetil in transplantation (2006)	MPA AUC: 30 to 60 μg/h/mL as determined by HPLC in the first 30 days posttransplantation (the upper limit is based on an absence of evidence for further reduction in risk of rejection >60 μg/h/L in patients receiving conventional doses of cyclosporine; there is no definitive upper range based on development of toxicity). MPA C_0: Renal ≥ 1.3 mg/L with cyclosporine and 1.9 mg/L with tacrolimus (HPLC)	In general, patients at higher risk of rejection may benefit from TDM to optimize MMF therapy. These include the following patients: receiving MMF in dual therapy (e.g.,MMF and calcineurin inhibitors but no steroids); not receiving induction therapy; receiving reduced-dose calcineurin inhibitors; receiving no calcineurin inhibitors; with delayed graft function and/or with delayed introduction of calcineurin inhibitors because of renal dysfunction without concurrent cytolytic therapy; with high panel reactive antibodies or evidence of donor-specific sensitization; with poor human leukocyte antigen match; with a repeat transplant; African American origin or other population at high risk of rejection; young children; adolescents (mainly to assess compliance); with altered gastrointestinal function and absorption; with hepatitis C (liver transplant); with T-tube post-liver transplant; with cystic fibrosis (lung transplant); with suspected drug interactions

(Continues)

TABLE 1 (Continued)

Recommendations	Target of MPA exposure	Indications of TDM of MMF
Kidney disease improving global outcomes (2009)	We suggest monitoring MMF levels. (2D) The proposed therapeutic window of the MPA $AUC_{0–12}$ (30-60 μg/h/mL) is restricted to the early posttransplant period and when MMF is used in combination with CsA. In general, MPA C0 1.0-3.5 mg/L correlates with MPA AUC_{0-12} (30-60 μg/h/mL) in patients treated with CsA	No data
Consensus report on therapeutic drug monitoring of mycophenolic acid in solid organ transplantation (2010)	The therapeutic window of 30 to 60 μg/h/L remains acceptable in patients who have low to intermediate immunologic risk and are on CNI-based therapy for the first 3 months after transplantation, with the lower limit of 30 μg/h/L being clearly associated with an increased risk for acute rejection As far as target therapeutic ranges are concerned, the situation will be different for recipients with high immunologic risk or in situations of CNI minimization/withdrawal, in which higher MPA exposure may be needed	In general, patients at higher risk of rejection may benefit from TDM to optimize MMF therapy. These include the following patients: Dual immunosuppressive therapy; Reduced-dosage CNI therapy (including delayed introduction of CNI); CNI switch or withdrawal; Recipients with high immunologic risk, Delayed graft function (renal, hepatic, bowel); Altered gastrointestinal/hepatic/renal function; Cystic fibrosis; Drug interactions; Noncompliance
Report of The Transplantation Society consensus meeting (2011)	Lack of the optimal target for all patients. Maintaining the same targets as 2006 consensus	Maintaining the same indications as 2006 Consensus using the categories below: High-risk patients; patients with delayed graft function; patients with immunosuppressive protocols excluding induction therapy or steroids or CNI; patients with CNI minimization
Interprofessional working group of the Canadian Society of Transplantation (2019)	The utility of TDM for dosing MMF and enteric-coated mycophenolate sodium remains controversial. Although there is significant between and within subject pharmacokinetic variability with these products, how exposure is best measured in clinical practice is unclear and TDM strategies are formulation specific. Data in kidney transplantation support a relationship between mycophenolate AUC and clinical efficacy (and to a lesser extent, toxicity); however, there are few studies in nonrenal transplant populations. Also, because the optimal means of performing mycophenolate TDM requires an abbreviated AUC measurement, it has not been implemented as part of routine care by many centers at this time Routine monitoring of mycophenolic acid serum levels is unnecessary regardless of brand or generic drug choice	No data

medication, and if necessary, discontinue it definitively. It should be noted that the intravenous (IV) administration of MMF is rarely used and reported in the field of solid organ transplantation (SOT). The studies showed that IV MMF provides significantly higher plasma concentrations, with higher peak concentrations and greater overall drug exposure, and higher AUC with increased risk of toxicity, in liver and KTs.[96,97] MPS, in its enteric-coated form was supposed to confer a better digestive tolerance digestive and fewer GI secondary effects, but the results have not shown a real benefit from MPS with a profile comparable to MMF.[48,98] However, the MPS is considered as an alternative to MMF therapy, offering physicians and their patients a new enteric-coated formulation of MPA with a comparable efficacy and safety profile to MMF.[99,100] Leukopenia and anemia are the main hematological complications observed with MMF. The incidence of anemia within the first year after KT reached 18.3% in patients using the combination of tacrolimus, corticosteroids and MMF 2 g daily, but with no statistically significant difference from the two other groups that received the same combination with MMF 1 g daily, or without MMF. The incidence of leukopenia however, was significantly different among the three treatment groups with a prevalence of 18.3% versus 6.1% in patients using MMF 2 g daily versus no use of MMF.[89] Leukopenia and anemia have been associated with high MPA $AUC_{0\text{-}12}$, high MPA C_0, high MPA free drug exposure, and high MPA metabolite concentrations in some, but not all studies.[78,101,102] Other adverse effects are also observed with MMF such as nervous system disorders (tremor, headache, and insomnia), infection (sepsis, urinary tract infection, and viral infection), angina, diabetes mellitus, and hypertension.[89] Infections, especially viral, comprise a major factor of morbi-mortality and loss of the graft among renal transplant recipients. The emergence of viral infections, mainly the BK virus (BKV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and parvovirus B19, have been closely linked to the use of strong immunosuppression, particularly the tritherapy association of mycophenolate, tacrolimus and corticoids.[103–105] Solid organ transplant recipients are also at increased risk of cancer, especially virus-related cancers, suggesting that the increase is due to loss of immune control of oncogenic viruses.[106] Safaeian et al analyzed the risk of colorectal cancer in US patients postsolid organ transplantation and did not observe elevated incidence of colorectal cancer in those treated with tacrolimus and MMF, as opposed to those treated with cyclosporine A and azathioprine posttransplantation.[107] This suggests the possibility of a beneficial effect of Mycophenolate vis-a-vis colorectal cancer. Indeed, some studies have shown the anticancer effect of mycophenolate against certain digestive cancers, notably colorectal and pancreatic. This is thanks to its antiproliferative properties and its ability to inhibit isoform 2 of IMPDH.[108,109] Another major point is the absolute contraindication to using MMF during pregnancy given the very high risk of severe malformations; MMF is highly teratogenic in humans.[110] This risk must be considered when prescribing for women of reproductive age and for sexually active men. Effective contraception should be used before beginning mycophenolic acids, during therapy and for 6 weeks following discontinuation of therapy, even when there has been a history of infertility. Will mycophenolate continue to be part of the postKT triple therapy, or will it be replaced by a new molecule, or by older ones such as the mammalian target of rapamycin inhibitors (mTORi), that are increasingly finding their place in KT, especially in smaller doses. A large and recent systematic review included 24 randomized clinical trials assessing the outcomes in 7356 KT recipients receiving mTORi + CNI compared with regimens containing MMF/MPA or AZA with CNI.[111] This systematic review did not show differences in acute rejection, mortality, or graft loss rates. The viral infections at any time and malignant neoplasia beyond 2 years were less frequent with mTORi-CNI. The rates of discontinuation because of adverse effects in the mTORi groups varied between 17% and 46% compared to 0%-26.6% in MMF/MPA groups.Notethat the current use of lower mTORi dosage has decreased the discontinuation rates.

1.5.2 | Drug-drug interactions

On examining the well-known drug interactions between MMF/MPS and other drugs, it is clear that many of these drugs are habitually used in the context of KT and that they lead to a decrease in MPA activity, hence the risk of MMF underdosage. This risk is particularly high and serious in patients at high immunologic risk, especially during the first posttransplant months. Among the well-known interactions, one finds CsA that inhibits the biliary excretion of MPAG and the enterohepatic recirculation. Consequently, patients treated with CsA usually require a higher dose of MMF than patients not treated with CsA.[112] The other medications that lower MPA activity include mainly proton pump inhibitors, corticosteroids, rifampicin, norfloxacin, antacids containing magnesium, and aluminum and cholestyramine.[113] The drugs, valaciclovir, widely used to prevent CMV infections, and sulfamethoxazole, widely used to prevent *Pneumocystis carinii* infections in KT, both have a leukopenia-inducing effect. Their association with mycophenolate increases this risk of hematologic toxicity.

1.6 | Generic molecules of MMF/MPS in KT

Immunosuppressive medication costs can be a substantial burden for transplant patients, potentially limiting access and increasing nonadherence. The use of therapeutically equivalent generic products can reduce financial burdens for recipients, payers, and healthcare systems, and improve the access to KT with great social and economic benefits. In the US and during the period 2008-2013, immunosuppression in KT was

marked by the increasingly frequent recourse to the brand name MMF and MPS with a decline in the use of generic MMF.[114] Despite that, the use of generic versions of MMF increased rapidly after their initial market; by 2013, 90% of prescriptions covered under Medicare Part D for MMF were dispensed as generics.[115] The first generic version of MMF was approved by the United States FDA in July 2008.[116] The first generic version of MPS, frequently prescribed as an alternative to MMF, was approved in 2012. Following a first switch from innovator to generic, no further substitutions from one generic to another should be performed. Therefore, it is best to prescribe a branded generic, that is, a generic drug that has a brand name, in order to specify which formulation should be dispensed to the patient. In addition, it is strongly recommended to avoid combining two molecules (brand and/or generic) of the same drug. Very few comparatives studies (MMF brand vs. MMF generic) have been conducted, but are limited (small sample size, monocenter) and have shown similar effects in terms of efficacy, tolerance, pharmacodynamics, and secondary effects between brand MMF and generic MMF.[117,118] The authors of a current meta-analysis about bioavailability, efficacy, and safety of generic immunosuppressive drugs for KT, showed that there was no significant difference between generic MMF formulations and brand MMF with respect to T_{max}, $T_{1,2}$, C_{max}, and $AUC_{(0\text{-}t)}$ of MPA.[119]

2 | CONCLUSION

After more than 20 years of use in KT, mycophenolate has proven its indispensable role as an immunosuppression maintenance drug. It is at the same time powerful, safe, and effective. Currently, more than 90% of KT recipients are given a combination of tacrolimus and mycophenolate and/or corticosteroids, an association that has made it possible to significantly reduce the incidence of acute post-transplant rejection and improve global kidney graft survival. It has, however, given rise on the one hand to chronic allograft nephropathy and on the other hand, fosters the occurrence of viral infections and malignancies. Although the TDM of MMF seems important to avoid under-or overexposure, it remains not particularly recommended and performed, given that any AUC of MMF above 60 µg/h/mL incurs the risk of toxicity, but especially increases the overall immunosuppression with all its consequences of infection and neoplasm. It is important to reason on the basis of risk, nondissociated, engendered by both tacrolimus and MMF and not based on an isolated tacrolimus risk first, and MMF secondarily. The TDM of MMF should take an important place in the follow-up of the KT recipient in order to establish targets according to the immunologic risk for the patient and to the post-transplant period. The high tacrolimus targets probably need to be counterbalanced by lower MMF targets. Can we move toward an individualization of AUC MMF targets based of immunologic risk and the global context of the patient?

CONFLICT OF INTEREST

The author declares that they have no conflicts of interest with the contents of this article

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