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Optimization of Therapy with Mycophenolic Acid After Kidney Transplantation

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Abstract

Mycophenolic acid (MPA) is the standard anti-proliferative agent used in transplantation today because of its efficacy and overall good tolerability. This review will focus on the adequate dosing of both available MPA formulations, enteric-coated mycophenolate sodium (EC-MPS) and mycophenolate mofetil (MMF). In particular, the optimal use of MPA in the initial period after transplantation and the potential utility of MPA-based regimens in maintenance patients are covered.

The active compound MPA is absorbed in the stomach (MMF) or small intestine (EC-MPS) and excreted biliary after hepatic glucuronidation. Because cyclosporine (CsA) inhibits enterohepatic recirculation of MPA, the MPA exposure in non-CsA-containing regimens is increased by 30-40%. This has to be considered for combinatory immunosuppression with tacrolimus (Tac) and mammalian target of rapamycin (mTOR) inhibitors. Proton pump inhibitors reduce MPA exposure in patients treated with MMF. Both formulations result in similar MPA exposure with potential minor differences in gastrointestinal (GI) side effects. MPA related side effects such as GI side effects, myelosuppression and infections often lead to dose reductions. It has been shown that MPA dose reductions are associated with inferior outcomes. As a consequence, physicians should aim at adequate MPA dosing after transplantation. Because MPA has no nephrotoxicity and no cardiovascular side effects, MPA is a favourable drug for the long-term treatment of renal allograft recipients.

In the initial period following transplantation high initial dosing is important to achieve adequate MPA exposure immediately after transplantation. MPA exposure of more than 30 μg*h/ml is thought to be necessary for effective rejection prophylaxis. In the initial period the risk for acute rejection is highest and therefore an adequate MPA exposure is essential. In cyclosporine-treated patients, only approximately 50% reach target MPA exposure. An initially intensified MPA dosing resulted in higher MPA exposure and lower rejection rates in several studies. The initial intensified dosing regimen, however, was not associated with more side effects and data from a meta-analysis showed overall comparable safety and tolerability to standard dosing.

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For maintenance immunosuppression MPA-based regimens may help to replace or diminish nephrotoxicity of calcineurin inhibitor (CNI) exposure and thus improve long-term graft and patient survival. Initial data suggest that CNI levels can be safely reduced when adequate MPA doses are given. CsA levels of 60-70 ng/ml and Tac levels of 3-6 ng/ml seem to be sufficient in combination with MPA in long-term maintenance patients for effective rejection prophylaxis and may help to reduce the CNI-associated side effects. In long-term maintenance (> 5 years posttransplant) even complete CNI withdrawal has been proposed in selected patients. Furthermore, in MPA- and CNI-treated patients, a successful steroid withdrawal has been suggested to diminish the severe side effects of steroids.

In conclusion, an optimized MPA-therapy after kidney transplantation has a potential to further improve outcomes after transplantation and to decrease some of the many side effects of current immunosuppressants. **(Trends in Transplant. 2011;5:3-12)**

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Key words

Mycophenolic acid. Enteric-coated mycophenolate sodium. Mycophenolate mofetil. Renal transplantation. Dose optimization.

Introduction

Renal transplantation is the best therapeutic option for patients with end-stage renal disease because it results in superior outcomes compared to dialysis[1]. In earlier times the main focus in transplant research was on better treatment and prophylaxis of acute rejections and by this means improving short-term survival. Due to a better understanding of underlying causes and a broadened arsenal of immunosuppressive drugs[2], the incidence of acute rejection episodes has fallen from around 50% to approximately 10% in the first posttransplant year[3] with one-year survival rates exceeding 90% in most centers[3].

Nowadays, the main focus has shifted towards improvement of long-term survival. Unfortunately, many immunosuppressive drugs increase cardiovascular risk factors (i.e. arterial hypertension, diabetes mellitus and hyperlipidemia), and aggravate underlying cardiovascular disease, a leading cause of death in transplanted patients[3,4]. An additional point of major concern is the CNI, which may contribute to chronic allograft failure[5]. Owing to the lack of nephrotoxicity, a neutral cardiovascular risk factor profile and its good efficacy, MPA is an integral part of all immunosuppressive regimens worldwide. This article will summarize the current knowledge on both MPA formulations (mycophenolate mofetil [MMF] and enteric-coated mycophenolate sodium [EC-MPS]), and aims to discuss novel MPA-based strategies to optimize long-term survival in renal transplantation.

Mycophenolic acid pharmacokinetics and pharmacodynamics

Mycophenolic acid inhibits the enzyme inosine monophosphate dehydogenase (IMPDH), which is essential for purine synthesis in proliferating lymphocytes[6,7]. Proliferating lymphocytes depend on the *de novo* pathway of purine synthesis and can not utilize the salvage pathway in contrast to most other cell types. Thus, MPA is thought to be a more specific antiproliferative agent compared

to azathioprine. Currently, MPA is available in two formulations: the prodrug MMF, launched in 1995, and EC-MPS, introduced in 2004[8,9]. Both formulations result in similar MPA exposure despite having different pharmacokinetic properties. Following absorption the pro-drug MMF is hydrolyzed into the active compound MPA in the gut, whereas EC-MPS is thought to dissolve in the small intestine at a pH above 5.5 due to the acidity resistant enteric coating impeding liberation in the stomach[10,11]. The MPA is absorbed rapidly and highly bound to plasma albumin[12] and it is glucuronidated in the liver and excreted biliary[13]. The concomitant immunosuppressive therapy containing CsA and high doses of steroids increases the rate of glucuronidation of MPA and thus reduces MPA-plasma levels[14-16]. Furthermore, CsA decreases the enterohepatic recirculation of MPA through inhibition of multidrug-resistance-2 transporters[17]. On the other hand, Tac, sirolimus, everolimus and belatacept have no impact on enterohepatic recirculation or glucuronidation[18,19] and 25-40% higher MPA exposure was observed in CsA-free regimens[12,20]. Recently it was found that proton pump inhibitors decrease MPA bioavailability in renal- and heart-transplanted patients receiving MMF but not EC-MPS by 30%[21-23].

An MPA-exposure in the initial period of > 30 µg*h/ml was found to be required for good efficacy in terms of avoiding acute rejections[12,24]. Studies comparing EC-MPS with MMF showed similar efficacy and safety of both formulations[9,10,25-27]. Major adverse events include gastrointestinal (GI) disorders like diarrhea, vomiting, abdominal pain and flatulence[11,28,29], infections and myelosuppression, resulting in anemia, leucopenia or thrombocytopenia[30-32].

Side effects from MPA therapy are frequent and may lead to dose reductions in up to 70% of patients in the first year after transplantation[9]. Similarly, some side effects may lead to patient non-compliance[10]. Inappropriate MPA exposure may result as a consequence of both dose reductions or non-compliance. Many retrospective studies have shown that MPA dose reductions and non-adherence to prescribed MPA therapy may lead to inferior outcomes: an increased risk of acute rejections[33-35], poorer long-term graft survival[36] and increased healthcare costs[35,36]. Many side effects that lead to MPA dose reductions are temporary and resolve completely. As a consequence, several investigators have tried to increase MPA dosage again in patients with previous dose reductions, in order to reach optimal MPA exposure[37]. The goal of optimal MPA doses was reached in a substantial number of patients in these studies, with no adverse impact on side effects, demonstrating the feasibility of this approach.

There is an ongoing debate whether EC-MPS has a smaller impact on GI side effects due to its enteric coating[10,11], and in some studies, the GI symptom burden seems to be alleviated after conversion from MMF to EC-MPS[38-41], but conclusive evidence from adequately powered blinded trials is lacking.

Several studies, including large registration trials, have shown a superior outcome of MMF compared with azathioprine regarding efficacy measured from biopsy-proven acute rejection when used in combination with CsA and glucocorticoids[42,43]. Although some studies question these findings in low-risk populations[31,32], MMF has replaced azathioprine in most centers and MPA is recommended as first-line antiproliferative agent in current guidelines[44-46]. In two registration trials EC-MPS was shown to have equivalent efficacy compared to MMF in combination with CsA and steroids[25,47]. Over the last decade Tac has replaced CsA as CNI in many centers, and the combination of Tac and MPA is the preferred drug regimen in many parts of the world. Despite its frequent use in combination with Tac, there is no adequately powered dose-finding study for the most frequent drug

combination used today. This is of particular importance as there is 30-40% higher MPA exposure with Tac compared to CsA, and this combination is the most prominent risk factor for the development of polyomavirus infection. Similarly, there are no dose-finding studies with new immunosuppressants such as belatacept[48], tofacitinib[49] or sotrastaurin[45,50] and evidence-based dosing recommendations for the combined use of MPA in combination with mTOR inhibitors (mTORi) are lacking.

In summary, MPA is today an integral part of standard immunosuppressive regimens worldwide[44,46], however its optimal use in different combination therapies is under discussion.

Initial immunosuppressive therapy

As the risk for an acute rejection is highest in the initial period after transplantation, initial immunosuppressive regimens are implemented at high doses. With standard MPA dosing, however, MPA exposure is lowest in the initial posttransplant period[9,24]. Many factors are responsible for this observation, including uremia, delayed graft function, surgery, poor absorption, and high initial CsA doses. Over the first 6 weeks MPA exposure increases under fixed dosing and stable exposure is reached after approximately 3 months. Many studies convincingly demonstrated an inverse relationship between MPA exposure and the incidence of acute rejections, especially in the early phase after transplantation[12,24]. In CsA-treated patients, less than 50% reach the recommended MPA exposure in the first month after transplantation[9,24]. There are two potential strategies to increase early MPA exposure: either an approach based on therapeutic drug monitoring or an initially intensified dosing scheme. It is important to point out that these strategies are not mutually exclusive, but may well complement each other.

The first strategy, a concentration-controlled approach with therapeutic drug monitoring, was tested in three well designed prospective trials. In the French APOMYGRE study, 130 renal transplanted patients were included. All patients had an induction with basiliximab and a subsequent triple therapy containing CsA, prednisolone and MMF. One group received fixed doses (FD) of 2 g MMF and the other concentration-controlled (CC) MMF doses for an intended target MPA exposure of 40 µg*h/ml starting on day 7. The MMF dose adjustments were made by a consulting service using a Bayesian forecasting. It is important to note that a few patients were already excluded from the analysis on day 7 and that the majority of patients had rather low MPA exposure in the first month, despite dose adjustments up to a mean of 2.9 g/day in the CC arm. There were no significant differences in the overall incidence of graft losses and adverse events between both groups. In the CC group, significantly less rejections occurred than in the FD group (12.3 vs. 30.7%; $p = 0.01$), however, a significantly higher incidence of herpes infection was noted in the CC group. The high rate of rejections in the control group was surprising in a standard quadruple regimen when comparing those results with the literature[9,51-55]. The second study, the FDCC-Study, was a large international trial with 901 patients, and compared two groups receiving MMF either in FD (2×1 g) or CC (intended MPA exposure 45 µg*h/ml) as determined locally from limited sampling strategies[52]. Again, a large number of patients in both groups were underexposed initially, despite an increase to 2.6 g/day MMF after one month in the CC group treated with CsA. Most importantly, MPA exposure correlated significantly with rejection, but only in the first month. In this large trial, no benefit was found for therapeutic drug monitoring. It was discussed that the range aimed for was missed in the CC group, blurring the theoretically existing differences of MPA exposure between the groups[52]. Physicians flinched from

increasing MMF dosages rapidly, based on single measurements, due to lack of experience at doses higher than 2 g/day. Furthermore, dose adjustments were based on the assumption of dose-proportionality, however recent data suggest non-linear MPA pharmacokinetics in the early period after transplantation[56]. The last study exploring the potential benefit of therapeutic drug monitoring investigated MMF trough levels to define the utility of concentration-controlled regimens[57]. 701 patients were equally randomized into one of the following three groups: concentration-controlled MMF with CNI either in reduced (group A) or standard dose (group B), or MMF fixed dose with standard CNI (group C). The MPA trough levels were targeted at 1.3 or 1.9 µg/ml for patients receiving CsA or Tac, respectively, but with a maximum dose of 4 g MMF. There was no difference between the groups regarding efficacy or safety[57], questioning the utility of MPA therapeutic drug monitoring as a way to improve MPA therapy.

An alternative approach to increase the number of patients reaching sufficient MPA exposure early after transplantation is the use of an initially intensified MPA dosing[52,54,58]. Three recent studies investigated this novel approach thoroughly and observed reduced rejection rates in patients treated with high MPA doses in the first weeks after transplantation. In the "OPTIMYZE trial", Glander, et al. reported first initial data on safety and provided a thorough analysis of pharmacokinetic profiles from 75 patients receiving a standard or intensified dosing regimen with EC-MPS in addition to CsA and corticosteroids following an induction with basiliximab. The standard group received 1.44 g/day throughout the study period, whereas in the intensified group the dosing was 2.88 g/day (until day 14), 2.16 g/day (day 15 to 42) and 1.44 g/day until the end. The recommended MPA exposure above 30 µg*h/ml was reached in 81.8% of the intensified group compared to only 40.7% ($p < 0.05$) in the standard group in the first week[54]. The IMPDH activity was significantly more inhibited on day 3 in patients with a MPA loading dose. In a follow-up of the second phase of this trial, Sommerer, et al. reported on a significantly better rejection prophylaxis with the intensified dosing regimen in 130 patients[55]. This result was confirmed in a meta-analysis with 441 patients combining the "Optimyze-trial" with an international study[9]. Patients randomized to a higher MPA dosing regimen had approximately 6% less rejections (13.8 vs. 19.8%) compared to a standard EC-MPS regimen with 1.44 g/day. Importantly, even in this large meta-analysis, the adverse event profile showed no marked differences between both groups[54] and GI tolerability was similar.

Lastly, a Canadian study ("CLEAR study") investigated early MPA exposure in 135 *de novo* renal transplanted patients[59] treated with Tac and an initially intensified MPA dosing scheme. In this study, patients were randomized to receive either 3 g (intensified) or 2 g (standard) MMF in the first 5 days and both groups received 2 g MMF until the end of study at month 6. They found a significantly higher MPA exposure on day 3 and 5 in the intensified group, and a very strong trend towards improved rejection prophylaxis (11.8 vs. 28.4%; $p < 0.055$) in the 3 g MMF group[59]. There were no significant differences regarding safety endpoints.

In summary, these studies strongly suggest that an intensified dosing of MPA in the initial immunosuppressive therapy leads to a better MPA exposure early posttransplantation and thus may help to prevent acute rejections, while there seems to be no additional burden on the frequency and intensity of side effects.

Maintenance immunosuppressive therapy

Despite being very potent in preventing acute rejection, CNI have many side effects,

including an elevation of cardiovascular risk factors and nephrotoxicity. Therefore, a major aim in transplantation medicine is to reduce, withdraw or completely avoid CNI in the maintenance period. MPA is devoid of nephrotoxicity and does not increase the cardiovascular burden. Thus, due to its safety profile and potency, MPA is the ideal drug for the maintenance phase. Many transplant physicians view MPA as an adjunctive agent in a CNI-based maintenance regimen. In contrast, we would propose the idea of a MPA-based immunosuppressive maintenance therapy, in which the more toxic substances, such as steroids or CNI, can be substantially reduced or even withdrawn. In the following paragraphs, we describe the initial emerging evidence for this approach.

Today there is good evidence that steroid-free protocols are feasible and safe in patients treated with CNI and MPA. In two meta-analyses, Pascual, et al. found no impact on graft survival after steroid withdrawal, despite a slightly higher non-significant rejection rate[60,61]. He concluded that steroid withdrawal after three to six months of combination therapy with CNI and MPA is very safe and efficient, with particular benefit in lipid profile[61]. The lower serum cholesterol in the steroid-free patients in combination with better blood pressure control and less glycemic adverse events is of particular interest as steroid withdrawal has the potential to modify several risk factors for cardiovascular morbidity[60]. Other benefits of steroid withdrawal include less bone, skin and eye problems, and fewer cosmetic side effects, which all might help to improve patient outcomes and compliance.

One of the first large, prospective, randomized studies investigating the potential CNI-sparing effects of MPA was published by a French group[62]. Frimat, et al. screened 101 long-term (on average 72 months posttransplant) renal allograft recipients on a CsA-based maintenance protocol without MMF. After randomization, patients either continued on their previous regimen or received 2 g MMF with half-dose CsA (MMF group). As expected, the 50% reduction of CsA levels to around 60-70 ng/ml resulted in a significantly improved allograft function. No rejections occurred in the low-dose CsA group with MMF. Apart from diarrhea and anemia being more frequent in the MMF group, all other safety aspects did not differ significantly, however approximately 25% of patients were withdrawn and did not tolerate MMF, mainly due to GI side effects. In a long-term follow-up, the safety was confirmed and the benefit in renal function preserved[62].

In a similar study by Pascual, et al. 64 stable renal recipients were observed 6 months after adjusting the immunosuppressive medication. One group remained on the standard dose of CsA, MMF and steroids, and in the other group CsA was reduced by 50%[63]. There were no rejections in both groups, but a significantly higher creatinine clearance was observed. Blood pressure, triglycerides, cholesterol and uric acid were significantly lower in the low CsA group[63].

In the "OLYMPE study", Kamar, et al. prospectively investigated the outcome in 94 stable renal transplanted patients in eight centers, who received Tac and MPA (either 1 g/day MMF or 720 mg/day EC-MPS) and steroids according to center practice[64]. Patients were randomized to either standard therapy with Tac and low-dose MPA (720 mg/day EC-MPS) or to high-dose MPA (1.44 g/day EC-MPS) together with low-dose Tac (trough level 2.0-4.5 ng/ml). The change in estimated GFR at month 6 was significantly higher in the high MPA group after substantial Tac reduction. The overall safety and efficacy was similar in both groups, and no rejections occurred in either group. Interestingly, glycemic control improved significantly after Tac reduction[64].

In conclusion, both studies demonstrate convincingly that adequate MPA therapy supports a substantial reduction in CNI exposure in stable long-term maintenance patients. From these trials, it seems that CsA levels of 60-70 ng/ml and Tac levels of 3-6 ng/ml are sufficient for effective rejection prophylaxis in combination with adequate MPA doses and that an MPA-based therapy has the potential to reduce the side effect burden of CNI.

Complete CNI avoidance with a MPA-based therapy in combination with basiliximab and steroids was not successful due to very high rejection rates[65]. Several large randomized studies investigated the potential of complete CNI withdrawal in the first 3 years posttransplantation under immunosuppression with MPA and steroids. All studies demonstrated substantially higher rejection rates, and Abramowicz, et al. found more acute rejection episodes and graft losses in the MMF plus steroid group compared with the CsA-based control group during the 4-year follow-up period[66]. In summary, CNI withdrawal is not advisable in the first 3 years post-Tx due to inferior long-term outcomes[66,67].

Calcineurin inhibitor withdrawal in long-term (> 5 years posttransplant) maintenance patients, however, was successful and safe in patients treated with MPA and steroids[68,69]. Both prospective randomized trials showed better renal function and no increased rejection risk after CNI withdrawal. In addition, other CNI-related side effects such as hirsutism and cholesterol were reduced in the CsA-free groups. In summary, CNI withdrawal in a MPA-based regimen with steroids added was only successful in long-term (> 5 years) maintenance patients, but not in the first 3 years posttransplantation.

Lastly, we will review briefly the potential utility of MPA in treatment regimens with mTORi and novel immunosuppressants. MPA is considered as a standard adjuvant immunosuppressant in CNI-elimination protocols using either mTORi or novel immunosuppressants such as belatacept[48,70], tofacitinib[49] or sotrastaurin[45,50]. While more data are needed for tofacitinib and sotrastaurin from ongoing phase II trials, belatacept has completed a large and comprehensive clinical trial program with more than 940 patients and up to 5 years of follow-up[48,53,70,71]. Until now, only standard doses of 2 g MMF were tested in combination with belatacept, basiliximab, and steroids. Patients in the belatacept treatment arm had approximately 40% higher MPA exposure compared to CsA-treated patients, although both groups were treated with similar MMF doses throughout the trial[53,71]. Despite significantly higher MPA exposure, patients did not experience more MMF-associated side effects. The CNI-free therapy with belatacept resulted in excellent renal function and preservation of kidney histology, however it was associated with more and severe rejections compared to standard therapy with CsA. An increased incidence of posttransplant lymphoproliferative disorder (PTLD) gives rise to concern and regulatory approval is pending. Since belatacept treatment was well tolerated, one potential way to improve efficacy in those regimens might be an initially intensified MPA dosing concept, which should be tested in future trials.

Another frequently used immunosuppressive therapy is the combination of MPA and mTORi[72-74]. Both substances have antiproliferative properties and overlap in their side effect profile, namely myelotoxicity and diarrhea. As already pointed out, this combination results in approximately 30-40% higher MPA exposure compared to CsA treated patients. The combination of both drugs allows early CNI withdrawal, as evidenced by the recently published "ZEUS trial"[73]. In this study, 300 patients were either switched from CsA to everolimus after 4.5 months or remained on CsA. The concomitant immunosuppression

containing EC-MPS and prednisolone was unchanged. Renal function calculated by the Nankivell formula was better in the everolimus group (71.8 ml/min) than in the CsA group (61.9 ml/min). The acute rejection rate was higher in the everolimus group (9.7 vs. 3.4%) and they had higher mean lipid concentrations, an increased urinary protein excretion and lower hemoglobin concentrations. Overall, MPA dose reductions due to side effects are frequent in this combination, and the optimal MPA dose in combination with mTORi needs yet to be determined.

In conclusion, MPA is the standard immunosuppressive agent lacking nephrotoxicity and a cardiovascular risk profile. In maintenance patients, an MPA-based therapy may help to avoid or at least reduce exposure to CNI and steroids and thus improve long-term allograft survival. The prerequisite for such an approach is, however, the tolerability of adequate MPA doses.

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