Trends in Transplant. 2008;2:51-61

Pharmacokinetics and Pharmacodynamics of Mycophenolic Acid: Different Formulations in Stable Renal Transplant Patients

Dario Cattaneo

Center for Research on Organ Transplantation "Chiara Cucchi de Alessandri and Gilberto Crespi", Mario Negri Institute for Pharmacological Research, Bergamo, Italy

Abstract

Mycophenolic acid has gained widespread acceptance as the antimetabolite of choice in most of the immunosuppressive regimens, thanks to its selective action versus T and B cells. This drug is characterized by a narrow therapeutic index and a well-documented relationship between efficacy (in terms of acute rejection episodes) and exposure to mycophenolic acid (as AUC and C_0). For these reasons, in the past years there has been an increased interest in the utility of monitoring mycophenolic acid concentration to optimize drug dosing.

Currently, two prodrugs of mycophenolic acid are available, namely mycophenolate mofetil and the enteric-coated formulation of mycophenolate sodium. Both formulations provide comparable distribution, metabolism and excretion of mycophenolic acid. However, important differences in drug absorption have been reported. Some of them were expected, being related to the enteric-coating film of mycophenolate sodium that delayed the absorption of mycophenolic acid, resulting in higher T_{max} values compared to those measured with mycophenolate mofetil. Nevertheless, a number of studies reported that the novel enteric-coated formulation of mycophenolic acid produced aberrant and extremely variable pharmacokinetic profiles, characterized by multiple peaks of mycophenolic acid concentrations and high basal drug concentrations. According to these preliminary data, mycophenolate sodium and mycophenolate mofetil cannot be formally considered as bioequivalent. Moreover, the growing body of literature on the importance of therapeutic drug monitoring of mycophenolic acid poses concerns also on the "clinical equivalence" between the two formulations. It is, indeed, very unlikely that all the monitoring strategies applied in the past years for mycophenolate mofetil could be applied in patients given mycophenolate sodium, due to the erratic and extremely variable absorption of the novel formulation. As an additional limitation, no data are available yet on the factors that could potentially affect

Correspondence to:
Dario Cattaneo
Unit of Pharmacology and Pharmacogenetics
Mario Negri Institute for Pharmacological Research
Via Camozzi, 3
24020 Ranica (BG), Italy
E-mail: dcattaneo@marionegri.it

the pharmacokinetics of mycophenolic acid released from mycophenolate sodium. Certainly, this information cannot be simply extrapolated from previous observations in patients given mycophenolate mofetil. As a support of this, it has been recently shown that the two mycophenolic acid formulations may be differently affected by concomitant therapies and/or comorbid conditions. As far as pharmacodynamic comparisons between mycophenolate mofetil and mycophenolate sodium, available data are too scanty to reach definitive conclusions, so that, at the present time, the monitoring of inosine monophosphate dehydrogenase activity (the pharmacologic target of mycophenolic acid) cannot be considered as a viable alternative to pharmacokinetic-based approaches.

In conclusion, evidences collected in more than 10 years of clinical use of mycophenolic acid have documented that this drug has important pharmacological properties that can be optimized by tailoring the best dosage for each patient according to periodical evaluations of the plasma levels. Nevertheless, this monitoring approach can, at the present time, be reliably applied only in patients on mycophenolate mofetil, but not in those treated with mycophenolate sodium. **(Trends in Transplant. 2008;2:51-61)**

Corresponding author: Dario Cattaneo, dcattaneo@marionegri.it

Key words

Mycophenolic acid. Pharmacokinetics. Pharmacodynamics. Organ transplantation. Pharmaceutical formulations. Bioequivalence.

Introduction

Since the introduction of cyclosporine to organ transplantation in the early 1980s, therapeutic drug monitoring has become an integral part of immunosuppressive agents[1]. These molecules are characterized by narrow therapeutic indexes, and therefore, small variations in the pharmacokinetic profiles may induce an inadequate level of immunosuppression, resulting either in increased risk to reject the graft, or magnification of drug-related adverse events[1]. These concepts apply to mycophenolic acid (MPA), an antimetabolite that, thanks to its selective action versus immunocompetent cells, has replaced azathioprine as part of the maintenance immunosuppressive therapies in most transplant centers. In fact, at variance with azathioprine that acts as a non-selective antimetabolite, MPA is a potent selective and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a key enzyme involved in the *de novo* synthesis of guanine nucleotides, which are critical for the proliferation of T and B lymphocytes[2], whereas other cell types (i.e. erythrocytes) can utilize alternative pathways (the salvage pathway).

Currently, two mycophenolate compounds are available, namely mycophenolate mofetil (MMF) and the enteric-coated mycophenolate sodium (EC-MPS). Both formulations act as prodrugs and are, therefore, characterized by the same mechanism of action. There are, however, some important differences in the pharmacokinetic properties that will be the topic of the present review.

Mycophenolate mofetil

Mycophenolate mofetil is the 2,4-morpholinoethyl ester of MPA. It is marketed for oral administration in capsules (250 mg), tablets (500 mg), or as powder for suspension. In some countries, MMF is available also as intravenous formulation as MMF hydrochloride (524 mg corresponding to 500 mg of MMF).

Following oral administration, MMF is absorbed rapidly and completely from the gastrointestinal tract and undergoes extensive presystemic de-esterification to MPA, the active moiety. In the whole blood, MPA is found exclusively in the plasma fraction, mainly bound to albumin, with a binding > 95%. *In vitro* and *in vivo* studies have consistently shown that only free MPA (the fraction unbounded to albumin) is capable of inhibiting IMPDH[2]. Mycophenolic acid is metabolized via glucuronidation in the gastrointestinal tract, liver and, to a lesser extent, in the kidney. Mycophenolic acid glucuronide (MPAG), the main metabolite, is a phenolic glucuronide of MPA with no pharmacologic activity. At least two other minor metabolites have been recently identified: the 7-0-glucoside and the acyl MPAG. More than 90% of the drug is excreted into the urine as MPAG via active tubular secretion. Following MMF administration, MPA T_{max} usually occurs 1-2 hours post-dose, with the appearance of a secondary peak at around 4-12 hours, attributed to enterohepatic recirculation of MPAG excreted into the bile, which is deconjugated back to MPA and reabsorbed in the colon through the action of glucuronidase shed by gastrointestinal tract bacteria. The mean elimination half-life of MPA ranges from 9-17 hours[2].

Mycophenolate sodium

Enteric-coated mycophenolate sodium (EC-MPS), the sodium salt of MPA, is available for oral use as a delayed-release tablet containing either 180 or 360 mg of MPA. This formulation was designed to improve MPA-related upper gastrointestinal adverse events by delaying the release of MPA until reaching the small intestine[3]. A study investigating the dissolution of EC-MPS tablets has shown that MPA is maximally released at a pH of 6.0-6.8 after 120 minutes, with results at pH 5.0 showing a slower and less complete release of MPA[4]. These data confirm that MPA is released from EC-MPS in the more alkaline environment of the small intestine, whereas the gastric absorption, if any, is negligible.

The processes of distribution, metabolism and excretion of MPA from EC-MPS are comparable to those reported for MMF[2]. There are, however, some peculiar characteristics in the drug absorption that are dictated by the nature of the formulation. In particular, studies in stable kidney transplant recipients treated with single doses of EC-MPS have documented MPA T_{max} ranging from 120-180 minutes, and variable half-life values varying between 5-8 hours[5-7].

Pharmacokinetic comparison between the two mycophenolic acid-releasing formulations

Two randomized, multicenter, clinical trials have shown that both in the *de novo* and in maintenance renal transplant recipients, the two MPA formulations were comparable in terms of efficacy and safety when given on fixed-dose regimens[8,9]. These evidences have led the transplant community to consider MMF and EC-MPS as "clinically bioequivalent". Accordingly, in clinical practice, 1,000 mg of MMF are considered equivalent to 720 mg of EC-MPS. Nevertheless, it should be stressed that "clinical equivalence" does not fully fit with the concept of "chemical equivalence". In fact, 1,000 mg of MMF delivers 2.31 moles of MPA, whereas 720 mg of EC-MPS corresponds to 2.24 moles of MPA. Although this difference could be considered minimal, it argues against the widespread misconception of bioequivalence between the two MPA formulations. Indeed, according to international consensus guidelines, two drugs can be considered as bioequivalent when they contain the same molecular entity, share an exactly equal qualitative/quantitative composition and identical pharmaceutical formulation.

Classically, demonstration of bioequivalence between two formulations requires specific pharmacokinetic evaluations, showing that the 90% confidence intervals of the relative main pharmacokinetic parameters (usually mean AUC and C_{max}) of the test to reference formulation would be within 80-125%. Looking in the literature, there are only few studies published in peer-review journals that have formally com-

pared the pharmacokinetics of MPA from EC-MPS with that released by MMF (as summarized in table 1). Overall, most of these studies have shown that limiting only to mean MPA AUC values, the two formulations could be considered as bioequivalent. This trend, however, was not confirmed when comparing the other main pharmacokinetic parameters (i.e. C_{max}, C_0, T_{max}).

In our clinical research center, we have recently conducted a comparative study involving kidney transplant recipients treated with EC-MPS or MMF for 24 months after surgery[13], with full MPA pharmacokinetic evaluations performed in both groups every six months. During all evaluations, aberrant and variable pharmacokinetic curves were found in patients who were given the novel enteric-coated formulation of MPA, whereas those on MMF had regular MPA kinetic profiles. Moreover, patients on EC-MPS presented extremely high C_0 concentrations, multiple peak of MPA, and T_{max} values ranging from 0-480 minutes, while those on MMF showed a sharp peak of maximum drug concentration always within 1-2 hours after drug intake (Figs. 1 and 2). To take into account potential bias related to patient selection, we decided to switch at month 24 after transplantation all kidney transplant recipients who were given EC-MPS to MMF. In this way, we found that the conversion resulted in a significant reduction in the MPA C_0 levels, with values comparable to those measured in patients who were given MMF throughout the study period. Notably, in patients who were shifted from EC-MPS to MMF, the atypical daily MPA profile did normalize, being associated with less variability in the main pharmacokinetics parameters (Fig. 1). These findings further indicate that the high variability in MPA absorption observed with EC-MPS was just linked to the novel formulation of MPA and not to potential bias in patient selection.

The emerging role of therapeutic drug monitoring

Both MMF and EC-MPS are usually administered at fixed daily oral dosages and therapeutic drug monitoring is not routinely performed. Nevertheless, recent evidence suggests that MPA pharmacokinetic monitoring could be advisable at least in patients treated with MMF (no data are available on EC-MPS). Accordingly, concentration-controlled approaches can be helpful to limit intrapatient variability of daily MPA exposure and to improve the clinical outcome of organ transplant recipients[16].

The first seminal study on this topic was published by van Gelder, et al.[17], in which 150 adult recipients of a primary or secondary cadaver kidney graft were randomly allocated to receive MMF treatment aimed at three predefined target MPA AUC values. Logistic regression analysis showed a highly statistically significant inverse relationship between MPA AUC (or MPA C_0) and the occurrence of a biopsy proven rejection, whereas this was not the case when using mean MMF dose. Subsequently, others have demonstrated important associations between MPA pharmacokinetics and graft function after kidney transplantation[18] or MMF-related adverse events[19]. Of particular relevance are the recent results of the French APOMYGRE trial[20]. In this 12-month study, 137 renal allograft recipients receiving basiliximab, cyclosporine, MMF, and corticosteroids were randomized to receive either concentration-controlled doses or fixed-dose MMF. A novel Bayesian estimator of MPA AUC based on three-point sampling was used to individualize MMF doses. The primary endpoint was treatment failure (death, graft loss, acute rejection, and MMF discontinuation). The study showed that at month 12, the concentration-controlled group had significantly fewer treatment failures (48 vs. 29%) and acute rejection episodes (8 vs. 25%) compared to patients kept on fixed MMF dose, confirming the clinical relevance of therapeutic MPA monitoring.

Taken together, all these evidences have led to the definition of provisional target therapeutic ranges for MPA AUC and trough concentrations to be applied in clinical practice. When combined with cyclosporin A (CsA), the recommended target ranges are 1-3.5 mg/l and 30-

Table 1. Summary of the studies that have compared the pharmacokinetics of mycophenolic acid from enteric-coated mycophenolate sodium and mycophenolate mofetil

Patients	Therapies	Study design	Main results	Comments	References
24 kidney transplant recipients	Cyclosporine Steroids?	Cross-over, single doses of EC-MPS or MMF	EC-MPS delivered bioequivalent mean MPA exposure (as AUC) compared with MMF	Patients were not on steady-state conditions Bioequivalence was not confirmed by C_{max} values	Arns, et al.[4]
32 heart transplant recipients	Cyclosporine Steroids?	Parallel groups	EC-MPS and MMF provided comparable mean MPA AUC values	Pharmacokinetic profiles were not presented Basal MPA values were not given	Yonan, et al.[10]
21 kidney transplant recipients	Tacrolimus	Conversion from MMF to EC-MPS	MMF and EC-MPS are associated with similar MPA exposure (as AUC)	Patients were at different time after transplantation Some but not all patients were on steroids Bioequivalence was not confirmed by C_{max} values	Budde, et al.[11]
18 kidney transplant recipients	Cyclosporine Steroids?	Parallel groups	Equimolar doses of EC-MPS and MMF produce equivalent MPA exposure (as AUC)	MPA levels were measured by EMIT assay Some but not all patients were on steroids Some kinetic profiles were estimated by LLS Bioequivalence was not confirmed by C_{max} values Patients with MPA C_0 > 10 mg/l were excluded	Budde, et al.[12]
32 kidney transplant recipients	Cyclosporine No steroids	Parallel groups for 24 months, then conversion from EC-MPS to MMF	Patients on EC-MPS had aberrant and variable MPA pharmacokinetic profiles characterized by high C_0 values and multiple peaks	Use of low-dose protocols Lack of cross-over evaluations No data from patients on tacrolimus	Cattaneo, et al.[13]
82 kidney transplant recipients	Cyclosporine Steroids	Meta-analysis including 3 studies with cross-over design	Bioequivalence between EC-MPS and MMF was found pooling the 3 trials together	Data on basal MPA values were not given Too much outlayers Some kinetic profiles were estimated by LLS	Johnston, et al.[14]
20 kidney transplant recipients	Cyclosporine Steroids	Parallel groups	EC-MPS delivered bioequivalent mean MPA exposure (as AUC) compared with MMF	Data on basal MPA values were not given Too much outlayers Some kinetic profiles were estimated by LLS Bioequivalence was not confirmed by C_{max} values	Johnston, et al.[14]

LSS: limited sampling strategies; MPA: mycophenolic acid; MMF: mycophenolate mofetil; EC-MPS: enteric-coated mycophenolate sodium.

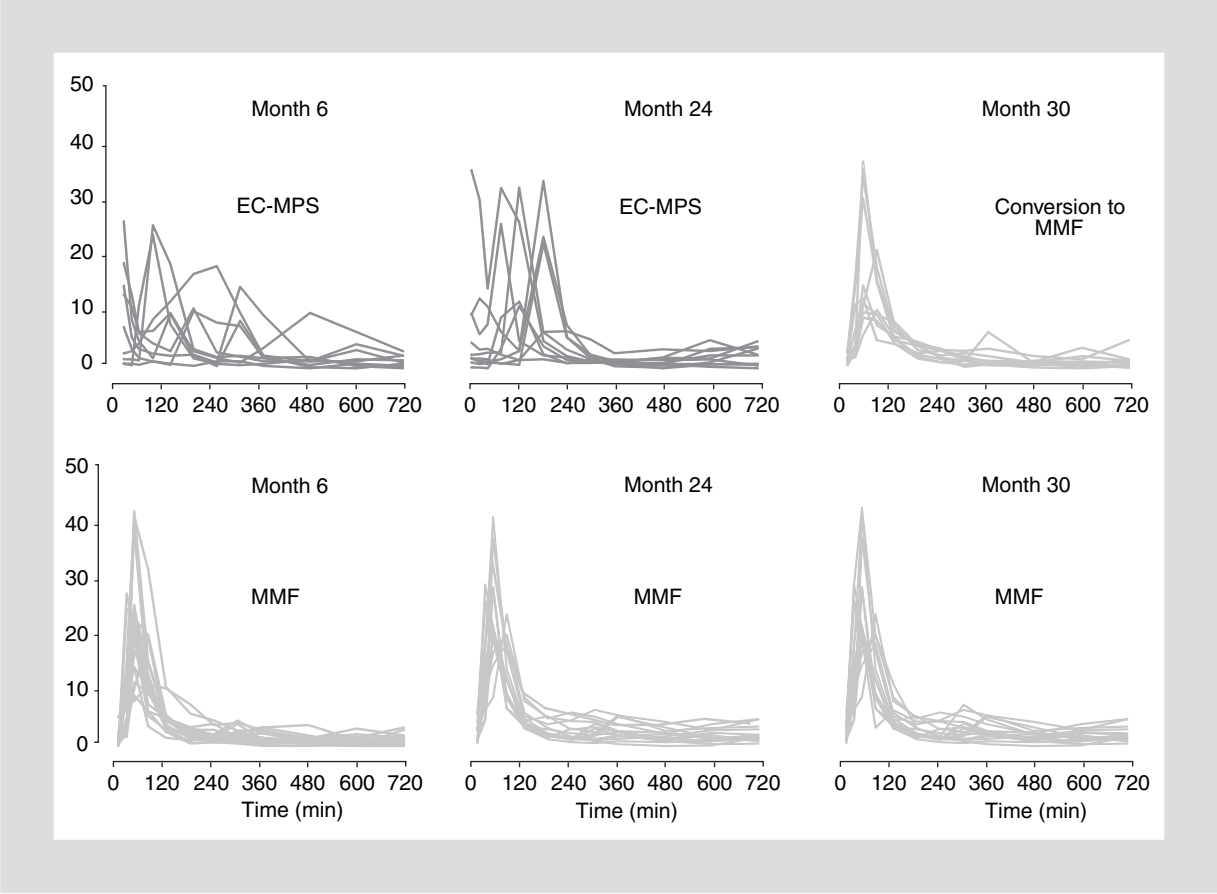

Figure 1. *Daily MPA pharmacokinetic profiles from kidney transplant recipients given EC-MPS or MMF as part of their maintenance immunosuppressive regimens. At the end of month 24 posttransplantation all patients on EC-MPS were shifted to MMF[13]. MPA: mycophenolic acid; MMF: mycophenolate mofetil; EC-MPS: enteric-coated mycophenolate sodium.*

60 mg·h/l for trough concentration and AUC, respectively. For the combination with tacrolimus, the suggested MPA target ranges are 1.9-4.0 mg/l for trough and 30-60 mg·h/l for AUC[16,21]. Nevertheless, it is of paramount importance to underline the fact that these ranges derive from studies involving patients treated with MMF, and therefore can be applied only with this formulation of MPA. At the present time, it is thus not possible to know whether the proposed therapeutic windows could apply also in patients on EC-MPS, simply because no therapeutic drug monitoring studies are available with the novel MPA formulation. On the other hand, indirect evidences are available suggesting that, for sure, patients given EC-MPS will not benefit from the monitoring of MPA C_0 concentrations as a guide to optimize drug therapy. Indeed, different studies have reported unexpectedly high MPA C_0 values in patients chronically given EC-MPS that, in some instances, exceeded 40 mg/l[13,22], whereas basal MPA concentrations measured in patients on MMF usually ranged from 1-8 mg/l. At the same time, others have documented comparable mean MPA C_{min} values between the two formulations[10,11]. It should be pointed out, however, that this discrepancy is only apparent, being mainly affected by the erroneous interchangeability of the terms C_0 and C_{min}. For this purpose, it must be remembered that the term "C_0" (or trough, basal) refers to the concentration of a given drug measured (in blood, plasma, or serum) just before the next medication dosage is given, whereas C_{min} represents the lowest concentration of a drug reached in the body between dosages. According to these definitions, the two parameters indicate different concepts, and therefore may not necessary coincide. As

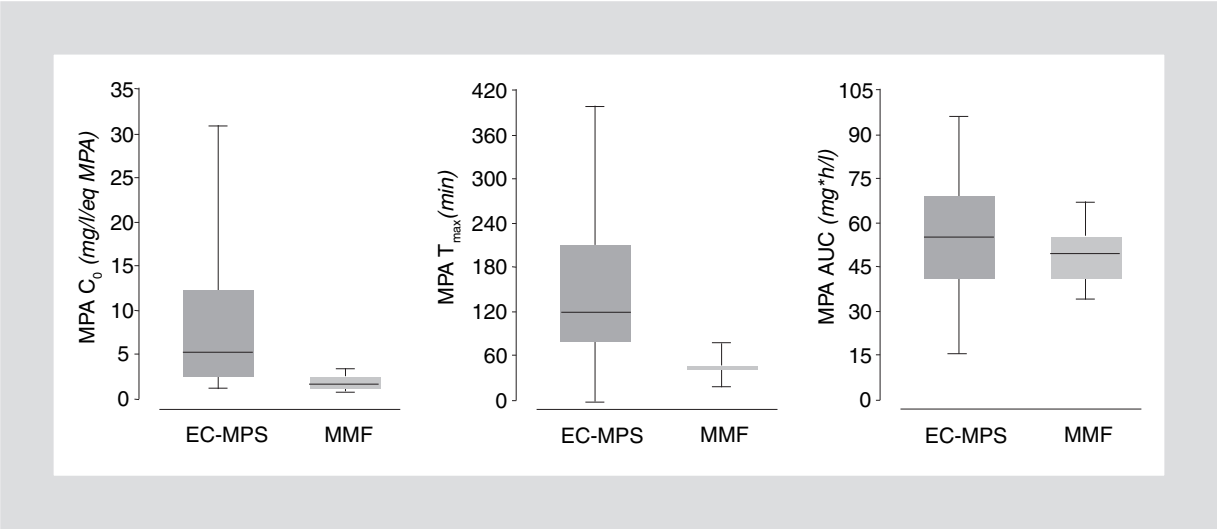

Figure 2. *Box-plot showing the distribution of the main MPA pharmacokinetic parameters (C_0, T_{max} and AUC_{0-12}) in kidney transplant recipients given EC-MPS or MMF[13]. MPA: mycophenolic acid; MMF: mycophenolate mofetil; EC-MPS: enteric-coated mycophenolate sodium.*

an example, in our study we found that EC-MPS presented comparable C_{min} values, but significantly different C_0 drug concentrations (Fig. 3). When using the right definition of basal drug concentrations, all the published studies consistently agreed that the novel enteric-coated formulation provided significantly higher MPA C_0 values than those measured in patients on MMF[12,13,22,23]. These differences may be relevant not only for pure pharmacokinetic disquisitions, but, eventually, also from a clinical perspective. In fact, it must be considered that the high concentrations of MPA C_0 observed in patients given EC-MPS do not parallel with increased AUC values[13], rendering the assessment of the former parameter, which is routinely performed in patients on MMF, totally useless and potentially harmful if applied in patients on EC-MPS because it might lead to erroneous dose adjustments with the potential risk of drug underdosing.

The issue of drug-to-drug interactions

Some important drug-to-drug interactions have been reported for MMF[2]. One of the most frequently observed interactions in organ transplant recipients involves the concomitant administration of cyclosporine and MMF. In particular, it has been demonstrated that cyclosporine inhibits its biliary excretion of MPAG by multidrug resistance associated protein 2 (MRP2) transporter[15]. This leads to impaired excretion of MPAG in the bile and reduced enterohepatic recirculation of MPAG, blunting the secondary peak of MPA normally seen when MMF was given in combination either with tacrolimus or sirolimus[15,24].

Nevertheless, it should be considered that findings on drug-to-drug interactions involving MMF cannot be automatically extrapolated also for EC-MPS. As a partial support of this statement, a randomized, calcineurin inhibitor crossover study has demonstrated that, at variance with previous observations with MMF[15], the switch between cyclosporine to tacrolimus (and *vice versa*) has only minor effects on MPA pharmacokinetics in stable renal transplant patients receiving EC-MPS[5].

Different effects of mycophenolic acid formulations on the pharmacokinetics of calcineurin inhibitors

The calcineurin inhibitors (CNI) cyclosporine and tacrolimus remain the backbone of immunosuppression for most organ transplant recipients. Both drugs are characterized by narrow

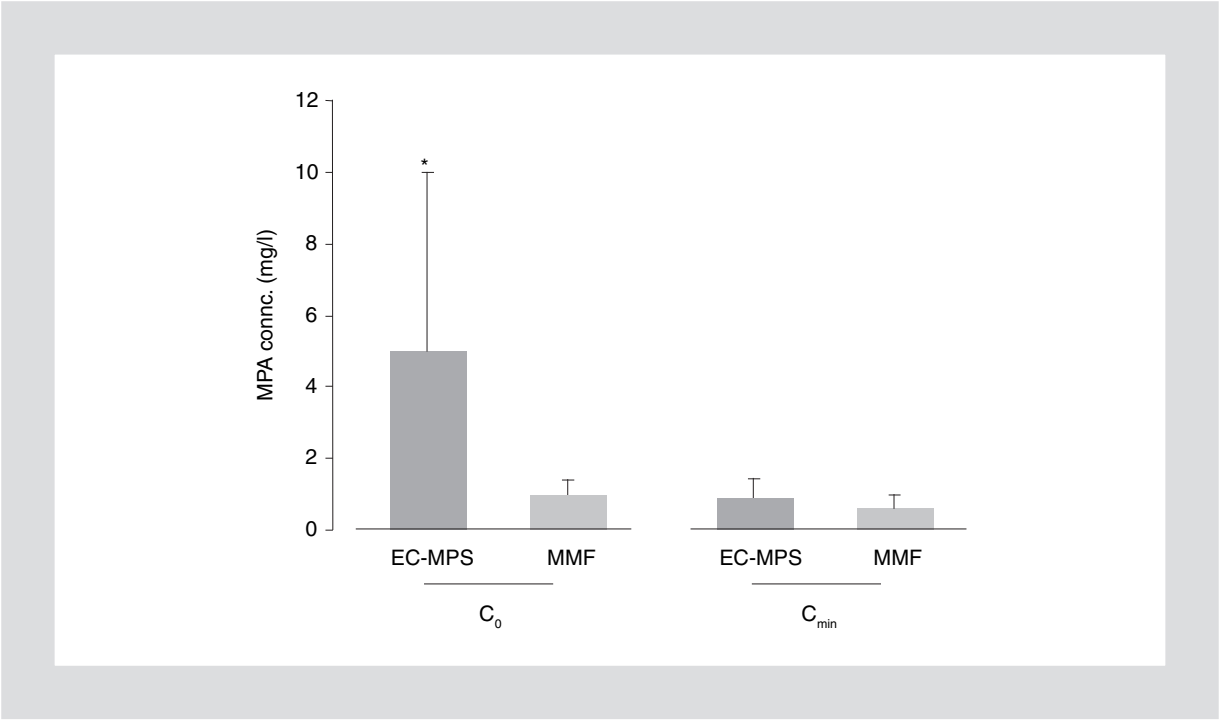

Figure 3. *Differences in the C_0 and C_{min} values observed in kidney transplant patients on EC-MPS or MMF[13]. MPA: mycophenolic acid; MMF: mycophenolate mofetil; EC-MPS: enteric-coated mycophenolate sodium.*

therapeutic indexes, irregular absorption, and high intrapatient variability in the daily drug exposure. Moreover, many investigations have consistently documented significant associations between the pharmacokinetics of CNI and the outcome of patients after transplantation, where low concentrations were associated with an increased risk for rejection, and high levels correlated with drug-related toxicity (reviewed[25]). Accordingly, therapeutic drug monitoring is routinely adopted in all transplant centers as a guide to tailor the best CNI dosage for each patient. For these reasons, it is likely that any factor able to significantly alter the daily exposure of cyclosporine or tacrolimus might have potential clinical implications.

In this regard, a comparative study involving kidney transplant recipients given cyclosporine in combination either with EC-MPS or MMF has shown that the MPA formulations significantly affected the pharmacokinetics of the CNI[26]. During all the kinetic evaluations, patients on EC-MPS had a shift to the right in the cyclosporine peak concentration as compared to that observed in patients given MMF, an effect associated with significant differences in T_{max} values. In particular, the authors found that the majority of patients on EC-MPS had cyclosporine peaking at two hours post-dosing, whereas most of patients on MMF had C_{max} at one hour. To assess whether these findings should be ascribed to EC-MPS or to MMF, we compared the pharmacokinetics of cyclosporine from these patients with those measured in patients given the CNI in combination with azathioprine[27]. As shown in figure 4, the pharmacokinetics of cyclosporine measured in patients given MMF or azathioprine were fully overlapped and differed significantly from the kinetic profiles observed in patients on EC-MPS, suggesting that the shift in the cyclosporine T_{max} was clearly related to the novel formulation of MPA. These findings would imply that cyclosporine C_2 values, recently proposed as a novel single-point monitoring strategy, may assume a different meaning according to the MPA formulation given concomitantly.

Notably, two independent studies have recently shown that simultaneous administration

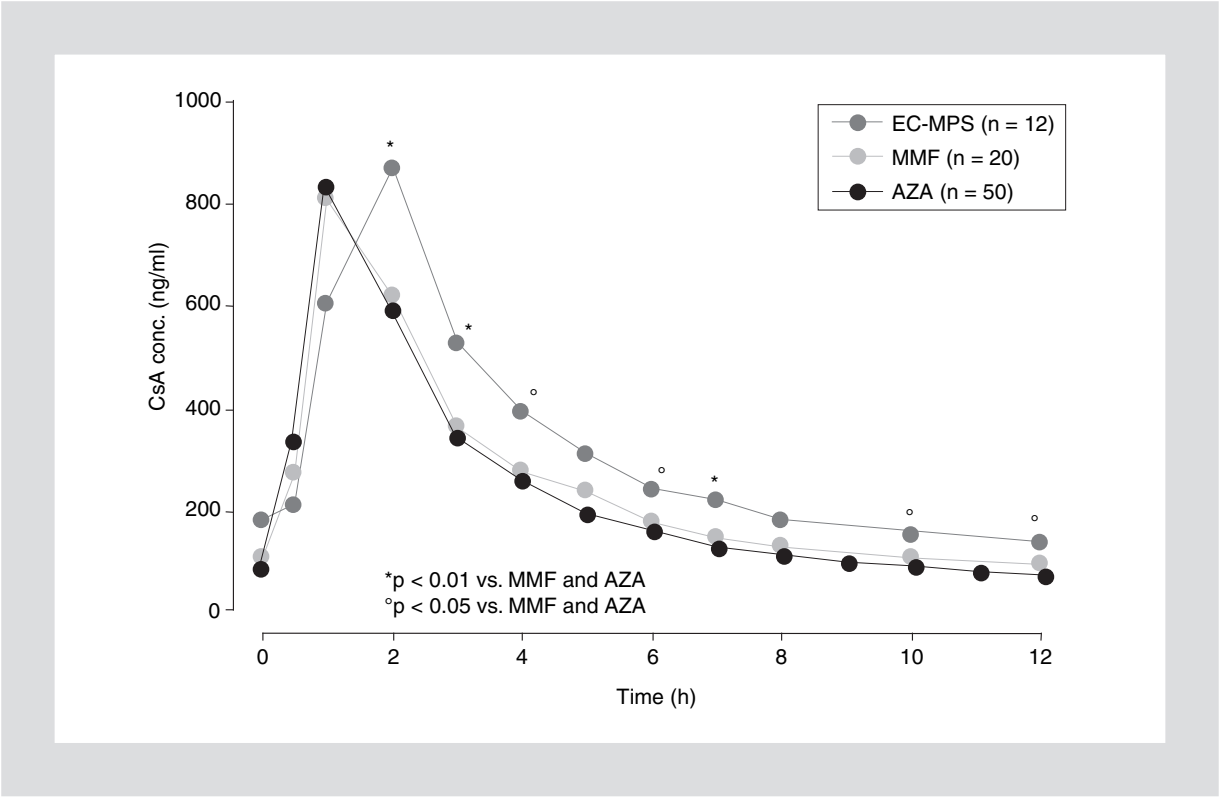

Figure 4. *Distribution in the daily CsA pharmacokinetic profiles in kidney transplant recipients given EC-MPS, MMF or azathioprine* (adapted from Refs. 26,27). *MMF: mycophenolate mofetil; EC-MPS: enteric-coated mycophenolate sodium; CsA: cyclosporin A; AZA: azathioprine.*

of EC-MPS induced significant alterations also in the pharmacokinetics of tacrolimus as compared with those observed with MMF[23,28]. Taken together, these results suggest that the novel formulation of MPA, probably due to its enteric-coated film, can significantly alter the absorption of both CNI. The clinical implications of these findings remain, however, to be established.

Pharmacodynamic monitoring of mycophenolic acid

Pharmacodynamic monitoring by measurement of IMPDH activity is a novel approach to individualize MPA therapy as it may better reflect biological response to the drug[2]. Nevertheless, the widespread application of this approach was limited by the complex methodology of the assay, which was technically demanding. These shortcomings have been overcome by the development of validated high-performance liquid chromatography (HPLC) methods able to estimate enzyme activity by measuring the rate of conversion of inosine monophosphate to xanthine monophosphate in PBMC, a reaction that is selectively catalyzed by IMPDH[29]. In the past few years, this assay has been applied in organ transplant recipients given MMF as part of their maintenance immunosuppressive regimens (reviewed[29]) with promising results. Remarkably, Glander, et al. have found that pretransplant IMPDH activity significantly correlated with clinical outcome after renal transplantation, both in terms of acute rejection episodes and complications of MMF therapy[30].

To date, only two studies have focused on the pharmacodynamics of MPA in patients given EC-MPS[11,12]. Both studies showed that maintenance renal transplant patients given tacrolimus or cyclosporine and converted from MMF to EC-MPS showed that the two MPA formulations provided comparable mean inhibition of IMPDH activity (approximately 85%). It should be underlined, however, that these studies reported a very large between-subject variability

in the IMPDH activity, a condition that might have potentially biased the conclusions. Moreover, as an additional drawback, only a very few patients were enrolled in the present investigations.

Due to the high variability in the results observed with both MPA formulations and the lack of validated *ad hoc* prospective clinical trials, the monitoring of IMPDH activity cannot be considered at the present time as a viable alternative to pharmacokinetic-based approaches.

Conclusions

Available data suggest that from a chemical-pharmacokinetic point of view, EC-MPS and MMF cannot be formally considered bioequivalent. Moreover, the growing body of literature on the importance of therapeutic drug monitoring of MPA poses concerns also on the "clinical equivalence" between the two formulations. It is, indeed, very unlikely that all the monitoring strategies applied in the past years for MMF, based on the measurement of basal MPA concentrations or on the prediction of the daily drug exposure (as AUC), could be applied in patients given EC-MPS due to the erratic and extremely variable absorption of the novel formulation.

As an additional restraint, no detailed data are available on the factors that could potentially affect the pharmacokinetics of MPA released from EC-MPS. At this stage this information cannot be simply extrapolated from previous observations in patients given MMF. In fact, preliminary evidences have shown that concomitant therapies may have a diverse influence on the two formulations of MPA[4,15]. Similarly, EC-MPS and MMF may be differently affected by coexistent pathologies, as has recently shown with diabetes, where the disease significantly altered the pharmacokinetics of MPA in patients given MMF but not in those on EC-MPS[31,32].

In conclusion, evidences collected during more than 10 years of clinical use of MPA have documented that this drug has important pharmacological properties that might eventually go beyond the immunosuppressive activity[33]. The use of this drug can be optimized by tailoring the best dosage for each patient according to periodical evaluations of the plasma levels. Nevertheless, this monitoring approach can only, at the present time, be reliably applied in patients on MMF but not in those treated with EC-MPS.

Acknowledgements

The Author is undoubtedly grateful to the *Foundation ART for Research on Transplantation Onlus* for the continuous support.

References

1. Oellerich M, Armstrong VW. The role of therapeutic drug monitoring in individualizing immunosuppressive drug therapy: recent developments. Ther Drug Monit. 2006;28:720-5.
2. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of mycophenolate in solid organ transplant recipients. Clin Pharmacokinet. 2007;46:13-58. ***A very comprehensive and updated review on the pharmacology of mycophenolic acid.*
3. Budde K, Glander P, Diekmann F, et al. Review of the immunosuppressant enteric-coated mycophenolate sodium. Expert Opin Pharmacother. 2004;5:1333-45.
4. Arns W, Breuer S, Choudhury S, et al. Enteric-coated mycophenolate sodium delivers bioequivalent MPA exposure compared with mycophenolate mofetil. Clin Transplant. 2005;19:199-206.
5. Kaplan B, Meier-Kriesche HU, Minnick P, et al. Randomized calcineurin inhibitor cross over study to measure the pharmacokinetics of coadministered enteric-coated mycophenolate sodium. Clin Transplant. 2005;19:551-8.
6. Ettenger R, Bartosh S, Choi L, et al. Pharmacokinetics of enteric-coated mycophenolate sodium in stable pediatric renal transplant recipients. Pediatr Transplant. 2005;9:780-7.
7. Perry TW, Christians U, Trotter JF, et al. Pharmacokinetics of enteric-coated mycophenolate sodium in stable liver transplant recipients. Clin Transplant. 2007;21:413-6.
8. Salvadori M, Holzer H, de Mattos A, et al. Enteric-coated mycophenolate sodium is therapeutically equivalent to MMF in de novo renal transplant patients. Am J Transplant. 2004;4:231-6. ** The first trial comparing the therapeutic effects of MPA formulations.*
9. Budde K, Curtis J, Knoll G, et al. Enteric-coated mycophenolate sodium can be safely administered in maintenance renal transplant patients: results of a 1-year study. Am J Transplant. 2004;4:237-43.
10. Hummel M, Yonan N, Ross H, et al. Pharmacokinetics and variability of mycophenolic acid from enteric-coated mycophenolate sodium compared with MMF in de novo heart transplant recipients. Clin Transplant. 2007;21:18-23.
11. Budde K, Glander P, Krämer BK, et al. Conversion from MMF to enteric-coated mycophenolate sodium in maintenance renal transplant recipients receiving tacrolimus: clinical, pharmacokinetic, and pharmacodynamic outcomes. Transplantation. 2007;83:417-24.
12. Budde K, Bauer S, Hambach P, et al. Pharmacokinetic and pharmacodynamic comparison of enteric-coated mycophenolate sodium and MMF in maintenance renal transplant patients. Am J Transplant. 2007;7:888-98.
13. Cattaneo D, Cortinovis M, Baldelli S, et al. Pharmacokinetics of mycophenolate sodium and comparison with the mofetil formulation in stable kidney transplant recipients. Clin J Am Soc Nephrol. 2007; 2:1147-55.
14. Johnston A, He X, Holt DW. Bioequivalence of enteric-coated mycophenolate sodium and MMF: a meta-analysis of three studies in stable renal transplant recipients. Transplantation. 2006;82:1413-8.
15. Hesselink DA, van Hest RM, Mathot RA, et al. Cyclosporine interacts with mycophenolic acid by inhibiting the multidrug resistance-associated protein 2. Am J Transplant. 2005;5:987-92. ** An experimental study providing the mechanism responsible for the interaction between CsA and MMF.*

16. Jeong H, Kaplan B. Therapeutic monitoring of mycophenolate mofetil. Clin J Am Soc Nephrol. 2007;2:184-91.
17. van Gelder T, Hilbrands LB, Vanrenterghem Y, et al. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral MMF for the prevention of acute rejection after kidney transplantation. Transplantation. 1999;68:261-6.
18. Cattaneo D, Gaspari F, Ferrari S, et al. Pharmacokinetics help optimizing MMF dosing in kidney transplant patients. Clin Transplant. 2001;15:402-9.
19. van Besouw NM, van der Mast BJ, Smak Gregoor PJ, et al. Effect of MMF on erythropoiesis in stable renal transplant patients is correlated with mycophenolic acid trough levels. Nephrol Dial Transplant. 1999;14:2710-3.
20. Le Meur Y, Büchler M, Thierry A, et al. Individualized MMF dosing based on drug exposure significantly improves patient outcomes after renal transplantation. Am J Transplant. 2007;7:2496-503. *** The first prospective randomized clinical trial documenting that therapeutic MPA monitoring can reduce the risk of MMF treatment failure and acute rejection episodes compared to fixed dose regimens.*
21. Shaw LM, Figurski M, Milone MC, et al. Therapeutic drug monitoring of mycophenolic acid. Clin J Am Soc Nephrol. 2007;2:1062-72. ** A position paper summarizing the actual evidence on the role of therapeutic drug monitoring of MPA.*
22. Budde K, Tedesco-Silva H, Pestana JM, et al. Enteric-coated mycophenolate sodium provides higher mycophenolic acid predose levels compared with MMF: implications for therapeutic drug monitoring. Ther Drug Monit. 2007;29:381-4
23. Sánchez Fructuoso A, Calvo N, Moreno MA, et al. Better mycophenolic acid 12-hour trough level after enteric-coated mycophenolate sodium in patients with gastrointestinal intolerance to MMF. Transplant Proc. 2007;39:2194-6.
24. Cattaneo D, Merlini S, Zenoni S, et al. Influence of co-medication with sirolimus or cyclosporine on mycophenolic acid pharmacokinetics in kidney transplantation. Am J Transplant. 2005;5:2937-44.
25. Schiff J, Cole E, Cantarovich M. Therapeutic monitoring of calcineurin inhibitors for the nephrologist. Clin J Am Soc Nephrol. 2007; 2:374-84.
26. Cattaneo D, Merlini S, Baldelli S, et al. Mycophenolic acid formulation affects cyclosporine pharmacokinetics in stable kidney transplant recipients. Ther Drug Monit. 2006;28:643-9. **The first paper documenting an impact of EC-MPS on cyclosporine pharmacokinetics.*
27. Cattaneo D, Gaspari F, Zenoni S, Gotti E, et al. Two-hour blood cyclosporine level does not necessarily predict drug exposure and graft function outcome in stable kidney transplant recipients. Therapy. 2005; 2:95-105.
28. Puig JM, Mir M, Marin M, et al. Significant pharmacokinetic differences between MMF and enteric-coated mycophenolate sodium in stable renal transplant patients treated with tacrolimus with or without steroids. Am J Transplant. 2007;7:349.
29. Weimert NA, Derotte M, Alloway RR, et al. Monitoring of inosine monophosphate dehydrogenase activity as a biomarker for mycophenolic acid effect: potential clinical implications. Ther Drug Monit. 2007;29:141-9.
30. Glander P, Hambach P, Braun KP, et al. Pre-transplant inosine monophosphate dehydrogenase activity is associated with clinical outcome after renal transplantation. Am J Transplant. 2004;4:2045-51. ** An important paper documenting a significant predictive role of MPA pharmacodynamic monitoring on complications of MMF therapy.*
31. Akhlaghi F, Patel CG, Zuniga XP, et al. Pharmacokinetics of mycophenolic acid and metabolites in diabetic kidney transplant recipients. Ther Drug Monit. 2006;28:95-101.
32. Patel CG, Richman K, Yang D, et al. Effect of diabetes mellitus on mycophenolate sodium pharmacokinetics and inosine monophosphate dehydrogenase activity in stable kidney transplant recipients. Ther Drug Monit. 2007;29:735-42.
33. Morath C, Schwenger V, Beimler J, et al. Antifibrotic actions of mycophenolic acid. Clin Transplant. 2006;20:25-9.