Enteric-coated mycophenolate sodium: role in transplantation

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This review outlines the mechanism of action of mycophenolic acid in transplantation. Its main side effects (gastrointestinal) often lead to dose reduction or discontinuation, which in turn carry the risk of graft failure. To overcome this problem, an enteric-coated version of mycophenolic acid has been developed. The authors, after having discussed the pharmacokinetics and pharmacodynamics of the compound, will review the main multinational trials. Finally, recent findings not yet published concerning the compound have been examined, as well as the possible use in nonrenal transplantation.

The reduction of acute rejection rates in renal transplantation has been achieved thanks to the use of powerful immunosuppressive agents such as mycophenolate mofetil (MMF). The main issue facing transplant activities is chronic rejection leading to graft loss and unwanted renal side effects related to some immunosuppressive agents, such as calcineurin inhibitors. Mycophenolic acid (MPA) appears, at least in part, to overcome such problems.

However, complications with the use of MMF are still observed, the most notable of which are gastrointestinal (GI) side effects. A new formulation (enteric coated [EC]) of MPA has recently been examined to overcome such problems. This paper describes the problems associated with both MMF and the EC formulation of MPA.

Mechanism of action of mycophenolate mofetil

Inhibition of lymphocyte proliferation

There are two pathways of purine synthesis: *de novo* and salvage. Lymphocytes are relatively deficient in their capacity to utilize the salvage pathway so they use mainly the *de novo* pathway. Inosine monophosphate dehydrogenase (IMPDH) is the predominant enzyme in the *de novo* purine synthesis pathway [1,2]. MPA is a potent, selective and reversible inhibitor of IMPDH. Thus, it inhibits only *de novo* purine synthesis (**Figure 1**) [1,3–5].

Two isoforms of the IMPDH enzyme have been characterized, each containing 514 amino acids, with 84% homology. IMPDH Type I is mainly expressed in resting lymphocytes. Both isoforms are upregulated in proliferating cells. *In vitro* and *in vivo* experiments have confirmed that MPA selectively inhibits the proliferation of B and T lymphocytes, with no effect on fibroblasts or endothelial cells, when administered at therapeutic levels [1]. In contrast to MPA, azathioprine nonselectively inhibits the proliferation of many cell types to a comparable degree; hence, bone marrow suppression occurs at doses close to those that are therapeutically useful [6]. Furthermore, MPA may have a strong inhibitory impact on antibody production by blocking B-cell proliferation [7].

In addition to its action on lymphocyte proliferation, MPA-induced deficiency of guanosine nucleotides inhibits the synthesis of glycoprotein adhesion molecules, such as selectins and integrins. MPA induces lymphocyte apoptosis and alters cell-surface and cytokine expression. Evidence has also been provided for the suppression of cytokine production by limiting the number of cytokine-producing cells [8,9] and for increasing apoptosis in lymphocytic and monocytic cell lines [10,11].

Other recently described biological actions of MPA, such as anti-inflammatory effects, make the drug a good candidate for use in many pathological conditions other then transplantation [12,13]. These anti-inflammatory effects have been linked to osteopontin inhibition [13], impairment of transendothelial migration of Tcells [14] and leukocyte inhibition of the inflammatory sites [15,16]. In addition, MPA was found to reduce macrophage- and leukocyte-derived cytokines as well as growth factors [17–20] and antagonize the activation of cultured human mesangial cells [21,22]. These mechanisms may contribute to observed attenuation of renal injury in various experimental models, such as ischemia/reperfusion injury [23], angiotensin II-induced hypertension [24], the rat remnant kidney model [25,26] and the prevention of glomerular injury in experimental diabetes [27].

Keywords: acute rejection, drug discontinuation, enteric-coated mycophenolate acid, gastrointestinal side effects, mycophenolate mofetil, patient compliance

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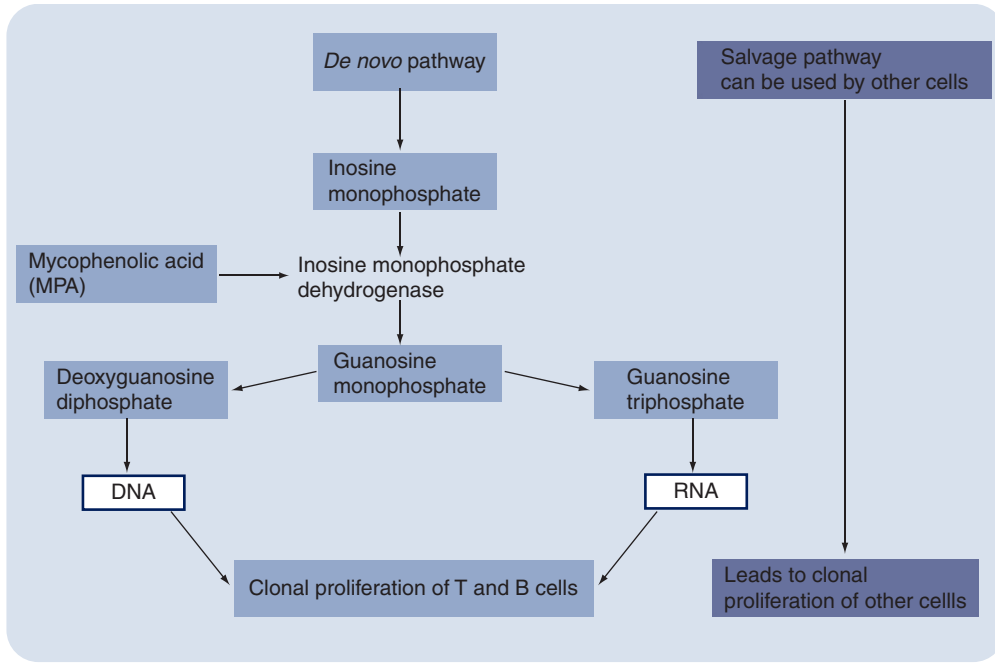
Figure 1. Mycophenolic acid inhibition of lymphocyte proliferation.



MPA in the clinical setting

MPA was first isolated from cultures containing *Penicillium* spp. [28] and was found to possess immunosuppressive activity when used in the treatment of psoriasis [29,30]. The potential of MPA as a new immunosuppressive agent in the field of transplantation is mainly based on its novel mode of action.

Furthermore, a synthetic derivative of MPA, MMF, was developed. *In vitro* studies demonstrated that MMF has powerful immunosuppressive qualities with low toxicity and a good safety profile [5]. Animal studies have evaluated the immunosuppressive qualities of MMF and have shown it to have a better oral bioavailability than MPA [31]. Both alone or in combination with other immunosuppressive agents, MMF has demonstrated potential in prolonging the survival of various organ allografts in several animal species, including heart allograft in rats and monkeys, aortic allograft in rats, pancreatic islet allograft in mice and rats and kidney and liver allografts in dogs [32,33].

MMF has been evaluated for the prevention of acute allograft rejection in three randomized, double-blind, multicenter trials involving almost 1500 adult renal transplant patients [34–36]. These trials were carried out in the USA, Europe and Australia, Canada and Europe. All of the studies included cyclosporin A (CsA) and corticosteroids in their immunosuppressive protocols. The USA and tricontinental studies compared MMF with azathioprine as an adjunctive immunosuppressant, and the European study compared MMF with placebo.

All of the above-mentioned studies demonstrated that MMF significantly reduces the incidence of biopsy-proven acute rejection or treatment failure at 6 months compared with azathioprine. Biopsy-proven acute rejection alone was reduced by approximately 50% in patients receiving MMF (13.8–9.8%) compared with those receiving azathioprine (35.5–38.0%), and by up to 70% compared with those receiving placebo (46.4%). According to Woodroffe and colleagues seven randomized, controlled trials compared MMF with azathioprine and confirmed that MMF reduced the incidence of acute rejection [37]. Three cost–effectiveness analyses compared MMF with azathioprine. Results consistently demonstrated that at 1-year post-transplant, MMF may be a cost-effective substitute for azathioprine in initial and maintenance therapy.

MMF also showed efficacy also over the long term in preventing chronic allograft nephropathy and therefore graft loss. This effect can be ascribed to the multiple mechanism of action of MPA mentioned above.

Ojo and colleagues documented a 4-year graft survival with MMF of 85.6% with respect to 81.9% of patients treated with azathioprine

($p < 0.001$), with a relative risk (RR) of 0.73 [38]. Meier Kriesche reported fewer late acute rejection with 65% of risk reduction for late acute rejection compared with aza ($p < 0.001$) in long-term treatment [39]. Notwithstanding, the relatively incidence of GI side effects reported in patients receiving MMF may limit its efficacy. Several investigators have retrospectively examined the outcome of patients, comparing those maintained on full MMF doses with those who either reduced the dosage of, or were withdrawn from, MMF.

In particular, in a retrospective study on patients treated with MMF (2 g/day) in conjunction with CsA and prednisone, Pelletier and colleagues documented that the majority of patients (70.3%, n = 507) had at least one dose change within the first post-transplant year [40]. Compared with the 214 patients who did not have a dose change, these patients had a much higher incidence of acute rejection within the first post-transplant year (23.3 vs 3.7%, $p < 0.001$). This resulted in a significantly decreased 3-year death-censored graft survival rate (66.3 vs 88.3%, $p = 0.003$). The incidence of acute rejection for patients who had a dose change was even higher if the dose change occurred within the first post-transplant month (34.4%).

Knoll and colleagues similarly determined whether MMF dose reduction after renal transplantation was associated with subsequent risk of acute rejection [41]. This retrospective cohort study assessed 213 renal transplant recipients. Cox regression was used to model MMF dose as a time-dependent variable, with time to first acute rejection as the primary outcome. A total of 162 patients (59%) had 176 MMF dose reductions during the study. MMF dose was reduced due to leucopenia (55.1%), GI symptoms (22.2%), infection (7.4%), malignancy (1.1%), and unknown reasons (14.2%). The cumulative number of days when the dose of MMF was reduced below the full dose represents was an independent predictor of acute rejection.

The RR of rejection increased by 4% for every week that the MMF dose was reduced below full dose. No significant association was observed between the number of days with MMF dropped below full dose and allograft failure.

In a US Renal Data System (USRDS)/Medicare retrospective analysis in patients with a functioning graft at 1 year, Hardinger KL and colleagues examined graft survival and cost following GI complications in renal transplant recipients treated with MMF [42]. GI complications or MMF discontinuation occurred in 27.4 and 17.5% of patients, respectively. MMF was discontinued in 21.3% of patients with GI complications and 16% of patients without ($p < 0.00001$). Graft survival of 4 years was reduced from 87.1–82.3% ($p = 0.091$) with MMF discontinuation, to 83% ($p = 0.001$) with GI complications and to 70.2% ($p < 0.0001$) with GI complications and MMF discontinuation.

Patients with GI side effects that discontinued MMF had a 53% higher cost than no GI MMF continuation patients, even if the cost of MMF was subtracted from the MMF discontinuation group (US$22,694 vs 14,799, $p = 0.0042$). Patients with GI side effects that continued on MMF also had 31.1% significantly higher cost than no GI MMF continuation patients (US$19,400 vs 14,799, $p < 0.0001$). Recently, a reduction in glomerular filtration rate (GFR) at 1 year has been associated with MMF discontinuation [43].

Enteric-coated mycophenolate sodium

Introduction to the compound.

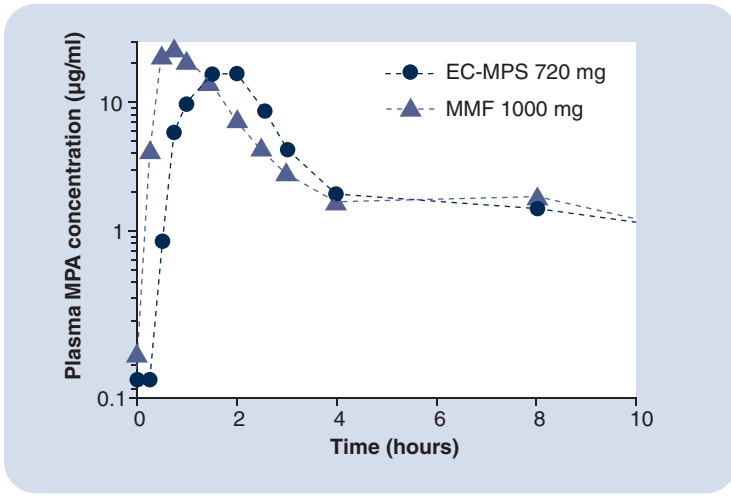
Even though some studies documented that intravenous application of MPA is also followed by GI side effects, indicating that these could be independent from the place of absorption, an EC mycophenolate sodium (EC-MPS) was developed to improve MPA-related upper GI adverse events (AEs).

The EC formulation of MPS delays the release of MPA. The EC remains intact in the acidic environment of the stomach and only dissolves once it reaches the pH neutral environment of the small intestine [44].

The choice of a formulation with release at approximately pH 6.0 was based on the following considerations. The first and primary concern was that myfortic would release in the stomach and not in the small intestine. Given the high tendency for renal transplant patients to develop gastritis due to multiple factors including uremia, steroids, calcineurin inhibitors and stress, a principle goal of the myfortic program was to ensure that MPA release from EC-MPS would consistently occur in the small intestine [45,46].

In addition, a number of renal transplant patients are treated prophylactically with low-dose proton pump inhibitors (PPIs); for example, in the pivotal study conducted in *de novo* transplant patients, the rate of PPI use was 40% [47]. Continuous gastric pH monitoring has shown that in the context of chronic PPI therapy (omeprazole 20 mg four-times daily) with a concomitant meal, maximum median gastric pH is approximately 5.5–5.0. Thus, in the context of renal transplant patients on PPIs, the choice of a release pH of 5.0–5.5 would have increased the probability of early release of

Figure 2. EC-MPS: delayed T_{max} consistent with MPA release in the small intestine.



EC-MPS: Enteric-coated mycophenolate sodium; MMF: Mycophenolate mofetil; MPA: Mycophenolic acid.

MPA in stomach. However, with the pH release features of the current MPA formulation, the authors estimate that even in renal transplant patients on prophylactic PPI therapy with concomitant meal, the majority of MPA release, greater than 70–80%, will occur in the small intestine.

Pharmacokinetics, pharmacodynamics & metabolism

As a consequence of the enteric coating and delayed absorption, EC-MPS and MMF have two different pharmacokinetic profiles (**Figure 2**). The curves for treatments are similar and show that MPA was rapidly absorbed. Absorption was faster for MMF than for EC-MPS, consistent with a functional enteric coating for EC-MPS. The pharmacokinetic parameters for MPA are shown in **Table 1** [44].

In this study, independently from large inter- and intrapatient variations, the pharmacokinetic parameters of the two drugs seem to be largely similar. In addition, the pharmacokinetic parameters measured for MPA glucoronide (MPAG), the main inactive metabolite of MPA, yielded similar values for both drugs.

Arns and colleagues reported a crossover study in which 16 renal transplant patients received single, variable doses of EC-MPS [48]. In this study, systemic MPA exposure and maximum MPA concentrations were both linear and increased proportionally with EC-MPS doses ($r^2 = 0.975$) [49]. Another study assessed the effect of food on MPA pharmacokinetics. After administration of EC-MPS, a high-fat meal had no effect on MPA area under the curve (AUC); however, there was a 33% decrease in C_{max} and a significant delay in T_{max} when compared with the fasting state. No effect of age on the pharmacokinetics of MPA and MPAG was documented by a study of 24 pediatric patients [50].

In a subgroup of patients receiving EC-MPS 720 mg twice daily as part of a large, randomized, double-blind study, systemic MPA exposure was assessed at 14, 90 and 180 days after initiation of treatment. The percentage of patients achieving or exceeding the target MPA exposure of 30 µg/h/ml at the three time point was 55, 86 and 100% with EC-MPS compared with 15, 76 and 72% with MMF, respectively (**Figure 3**). Importantly, the incidence of AEs was similar for both treatment groups [51]. Thus, in this subgroup, EC-MPS rapidly achieved the target therapeutic exposure of MPA (30 µg/h/ml), without an increase in adverse effects.

Considering that the efficacy of immunosuppressive agents can be deeply modified by drug interactions, several studies have been carried out on EC-MPS interaction with other drugs. The main results of these studies are:

- At steady-state, mycophenolate sodium delayed release did not affect the pharmacokinetic of CsA [52]
- In stable renal transplant recipients treated with mycophenolate sodium delayed-release, MPA plasma exposure was increased by 19% in patients receiving concurrent immunosuppression with tacrolimus versus CsA-microemulsion (ME) [53]
- The coadministration of antacid decreased the mean MPA AUC and C_{max} by 37 and 25%, respectively [52]
- Levels of acyclovir and gancyclovir (and MPAG) are increased if these agents are co-administered with mycophenolate sodium delayed-release in patients with renal impairment [52]
- Concurrent administration of mycophenolate sodium delayed-release and a bile acid sequestrant, such as cholestyramine, interrupted enterohepatic recirculation and reduced MPA exposure [52]

Preclinical data

In preclinical studies in rodent transplantation models, minimal efficacious doses of MPS were related to first signs of adverse effects, indicating a narrow therapeutic window. There was no poten-

Table 1. Summary of plasma mycophenolic acid pharmacokinetic results.

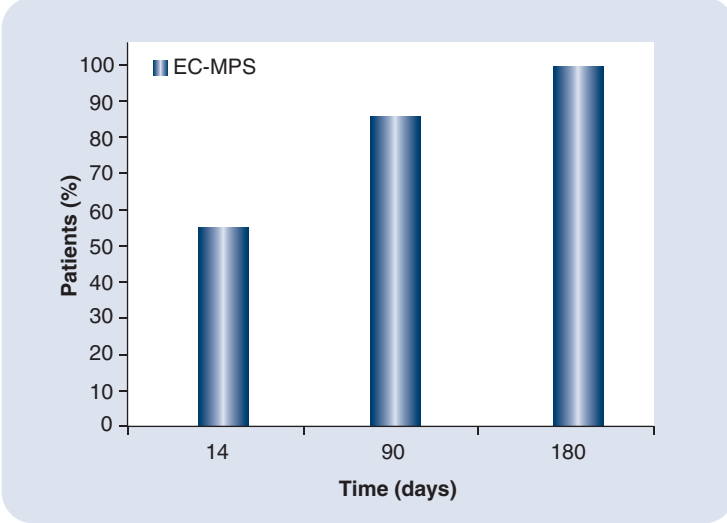
Formulation	Compound mass	Dose (MPA) equivalent (mg)	T_{max} median (h)	C_{max} mean (µg/ml) (CV%)	$AUC_{0–12}$ mean (µg h/ml) (CV%)
MMF 250 mg capsule	250.0 mg moefil ester	739	0.75	30.2 (47%)	63.7 (24%)
EC-MPS	384.8 mg sodium salt	720	2.0	26.1 (47%)	66.5 (34%)

AUC: Area under the time–concentration curve; EC-MPS: Enteric-coated mycophenolate sodium; MMF: Mycophenolate mofetil; MPA: Mycophenolic acid.

tial synergy between CsA and MPS or MMF with respect to the efficacy, but fewer adverse effects were noted in combination with mycophenolate sodium. Monotherapy of MPS was better tolerated than MMF in some of the transplant models [54].

MMF and EC-MPS were investigated in beagle dogs. All placebo-treated dogs appeared healthy, whereas 75% of MMF- and 100% of EC-MPS-treated dogs developed GI AEs. Histologically, animals with diarrhea had enteritis and colitis with scattered foci of cryptitis and/or crypt abscesses. MPA AUC at 12 h and C_{max} were higher in MPS-treated dogs, and MPA AUCs revealed high interindividual variability. However, the enteric coating of MPA neither reduced the incidence of diarrhea, nor avoided intestinal mucosa abnormalities, as seen with MMF [55]. It is noteworthy to outline that the author in this study used a different EC formulation with respect to those actually on the market. In addition, all these studies were conducted on a small number of animals; therefore, it is difficult to draw definitive conclusions. More recently, from an efficacy point of view, a study in nonhuman primates demonstrated for the first time that the immunosuppressive effect of MPS given at a threshold immunosuppressive dose in association with FTY720 (fingolimod), at a lymphopenic but not immunomodulatory dose, markedly potentiated the survival of kidney allograft.

Figure 3. Area under the time–concentration curve for MPA.



Percentage of patients with mycophenolate acid (MPA) AUC > 30 µg h/ml at different time points. EC-MPS: Enteric-coated mycophenolate sodium (ERL080).

Rationale for developing EC-MPS & objectives for clinical development

Due to the high incidence of GI side effects that often lead to dose reduction of MMF, a strategy was developed to realize an alternative delivery form, an EC tablet would provide:

- Therapeutic equivalence to MMF
- Smaller tablets that might improve patient compliance
- Potential for improved GI tolerability and fewer dose reductions

The main chemical characteristics of the two compounds, MMF and EC-MPS, are shown in **Figure 4**.

Clinical pharmacology studies

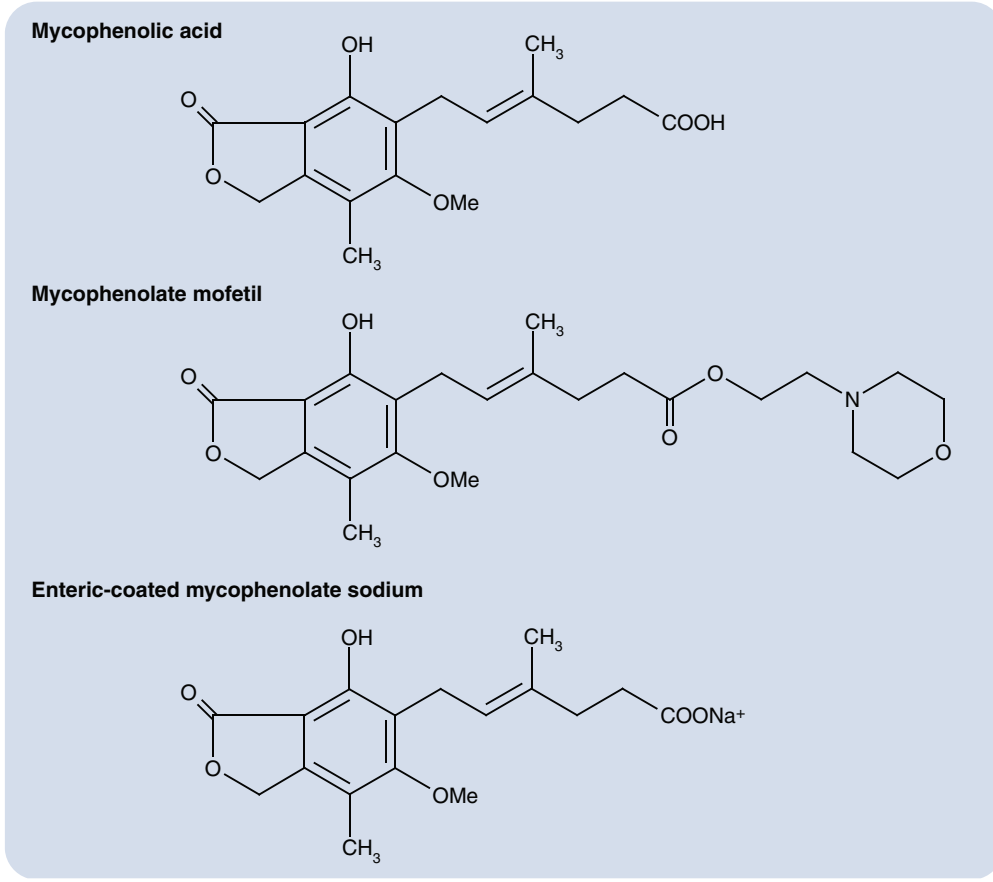
Several clinical pharmacology studies were conducted which established that 720 mg of sodium MPA was equivalent to 1000 mg of MMF in terms of exposure [44,48].

Phase III registration studies

Two double-blind, placebo-controlled studies were conducted and were the basis for the registration of EC-MPS in Europe and the USA.

A Phase III, 12-month, international (30 centers), randomized, double-blind, parallel-group study in 423 patients undergoing *de novo* renal transplantation was performed to evaluate the therapeutic equivalence of EC-MPS and MMF [47]. The disposition of patients in the two treatment groups throughout the 12-month study was similar. The incidence of study drug discontinuation was similar to that observed in other blinded studies [35,36]. Patients who had received a

Figure 4. Chemical structures of mycophenolic acid (MPA), the morpholinoethyl ester of MPA, mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS).



primary, cadaveric, or living unrelated or human leukocyte antigen (HLA)-mismatched living, related donor organ were enrolled. Previous recipients of a kidney or another organ, or multiorgan recipients, were excluded. Patients received EC-MPS 720 mg twice daily (n = 213) or MMF 1000 mg twice daily (n = 210) plus a standard immunosuppressive regimen of CsA-ME and corticosteroids for 12 months.

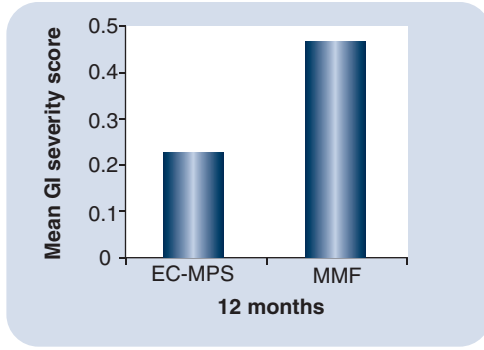
For all patients, the primary efficacy evaluation was treatment failure – a composite variable comprising biopsy-proven acute rejection (BPAR), graft loss, death, or loss to follow-up within 6 months of the start of treatment. The two-sided 95% confidence interval of the different event rates between the EC-MPS and MMF groups had to be entirely within the predetermined interval (±12%) to conclude equivalence. Secondary end points included evaluation of the overall efficacy and safety profile, including the incidence of AEs (GI side effects, infection and malignancies), at 6 and 12 months [47].

The incidence of efficacy failure at 12 months was similar in the two groups documenting the therapeutic equivalence. The incidence of BPAR was also comparable between the treatment groups at 12 months (EC-MPS 22.5% vs MMF 24.3%). In patients who experienced BPAR, the proportion of mild acute and moderate acute episodes were comparable between treatment groups, whereas severe BPAR episodes were lower in the EC-MPS group (1.9 vs 7.1%; p = not significant) [56].

Concerning safety, the overall incidence of AEs was comparable in both groups at 12 months. Although the incidence of GI AEs was comparable in both treatment groups throughout the study, GI AEs led to the discontinuation of study medication, dose reductions, or temporary interruptions in 15% of patients on EC-MPS and 19.5% in patients on MMF.

The second Phase III study was a double-blind, 12-month study to investigate whether renal transplant patients taking MMF can be safely converted

Figure 5. Mean changes from baseline in GI adverse event severity score at 12 months (B302 study).



EC-MPS: Enteric-coated mycophenolate sodium; GI: Gastrointestinal; MMF: Mycophenolate mofetil. p = not significant.

to EC-MPS [57]. Stable kidney transplant patients were randomized to receive EC-MPS (n = 159) or to continue receiving MMF (n = 163). The incidence of GI AEs was similar at 12 months (EC-MPS: 29.6%; MMF: 24.5%). Moreover, in this study, the changes from baseline for GI AEs were evaluated by a severity score at 3.6 and 12 months. The severity scores for all GI AEs were recorded as 0 for no event, 1 for mild, 2 for moderate and 3 for severe. For each patient, the individual scores, weighted by duration, were summed to obtain a total severity score. The increase from baseline in mean GI AEs (AEs) severity score, adjusted for duration, was lower in EC-MPS patients (0.23 vs 0.47 at 12 months) (**Figure 5**).

In this study, the efficacy was evaluated as a secondary end point. Similar to the previously described study, similar rates of efficacy failure were observed in both groups. However the Kaplan–Meier point estimates of the probability of experiencing BPAR, graft loss or death at 12 months of the initial dose of study medication, were 2.7% for EC-MPS and 8.7% for MMF. Log rank analysis did not show a statistically significant difference between the two Kaplan–Meier curves.

Both studies had an open-label extension part where all patient were to receive EC-MPS. The former reported the first long-term safety and efficacy data on EC-MPS when administered for up to 3 years post-transplantation [58]. Of 367 patients completing the blinded core study, 247 (62%) entered the open-label extension phase (**Figure 6**). During the first 24 months of the extension, the incidence, type or severity of AEs were comparable between the newly-exposed and long-term EC-MPS patients. Cross-study comparisons indicated that the tolerability profile of EC-MPS and MMF was similar, including the incidence of AEs, infections and malignancies, as was the incidence of efficacy events. These results demonstrated that EC-MPS with CsA and steroids provides good efficacy with an acceptable long term safety profile, and confirm the safety of converting renal transplant patients from MMF to EC-MPS.

In the open-label extension of the latter study, it was shown that conversion of maintenance renal transplant patients from MMF to EC-MPS is safe, with similar efficacy. During this 12-month, open-label extension study, the type, incidence and severity of AEs were similar to that observed during the first 12 months post-transplant within the core, double-blind trial, both among patients receiving EC-MPS from the time of transplant and those converted from MMF to EC-MPS at the end of the core study. Incidence-related events later were low and comparable between EC-MPS long-term patients and those converted from MMF. These data confirm the long-term safety of EC-MPS as well as the safety of converting MMF maintenance renal transplant patients to EC-MPS [59].

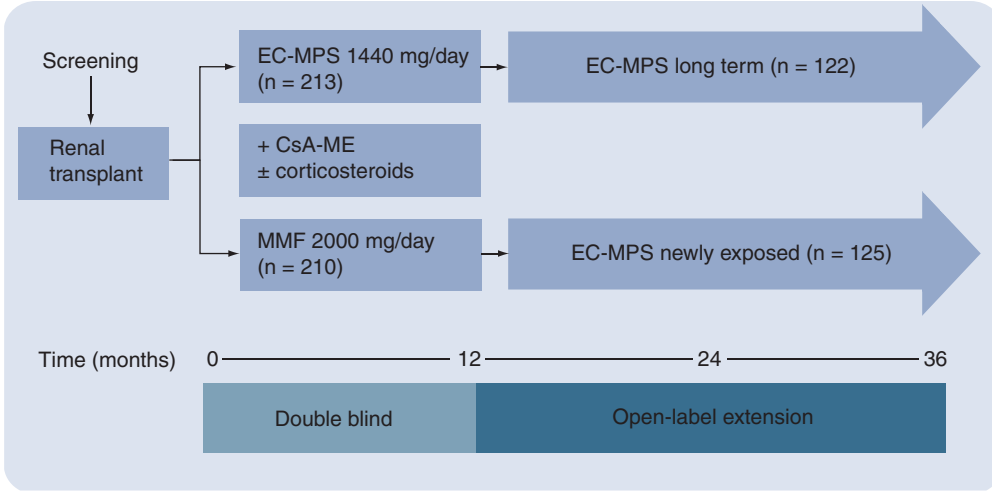
Phase IIIb, Phase IV & postmarketing studies

The previously described results of EC-MPS have been confirmed by several smaller studies in which EC-MPS was used in different immunosuppressive regimens or in different conditions.

Cibrik and colleagues documented the EC-MPS efficacy and safety in high-risk patients [60]. EC-MPS was given in combination with Neoral, simulect and steroids. The high-risk population in this study had at least one of the following characteristics: black recipients, recipients of less than 60 years, donors of less than 55 years, prior transplantation, nonheart-beating donors and panel reactive antibodies (PRAs) of less than 35%. The BPAR rate, 20.4%, was acceptable for this high-risk population. In terms of safety, AEs thought to be related to the study drug by investigators were hematologic (15%), infectious (12%) and GI (25%).

In another study, EC-MPS was given in combination with basiliximab, steroids and either full- or reduced-dose CsA in *de novo* kidney transplant recipients [61]. Incidence of BPAR were 17.8% in the full-dose group and 15.9% in reduced-dose group at 12 months, without any difference in the time to first acute rejection. Creatinine clearance was 57.2 ± 22.3 ml/min in the full-dose and 51.2 ± 25 ml/min in the reduced-dose group at 12 months. These data indicate that a regimen of low-dose CsA in combination

Figure 6. Study design (ERL B301) .



CsA-ME: Cyclosporin A microemulsion; EC-MPS: Enteric-coated mycophenolate sodium; MMF: Mycophenolate mofetil.

with basiliximab, EC-MPS and steroids has an excellent therapeutic effect and is safe in *de novo* kidney transplant recipients.

Other studies show the possibility of steroid withdrawal in the context of EC-MPS, CsA and steroids immunosuppressive regimen in *de novo* renal transplant recipients. Walker and colleagues reported an interim analysis of a 12-month study, performed at 3 months from transplantation . The objective was to evaluate the clinical outcome of using no steroids or short-course steroids versus standard steroid therapy. Patients were randomized to one of three steroid regimens:

- Steroid-free
- Steroid withdrawal (day 1–3 *in vitro* steroids; day 4–7 oral steroids)
- Standard steroid dosage

The interim analysis concluded that:

- BPAR in patients on standard steroid therapy who did not experience delayed graft function was exceptionally low
- AEs and serious AEs were similar in the three treatment groups
- BPAR in the steroid-sparing arms must be balanced against the reduced potential for steroid-related AEs

The safe conversion to EC-MPS from MMF in stable renal transplant has also been documented also by a multicenter Asia–Pacific study [63]. The objective of the study was to assess safety parameters and graft function in maintenance renal transplant recipients and to assess the efficacy evaluating the incidence of acute rejection episodes (AREs) and graft survival. Study conclusions were that:

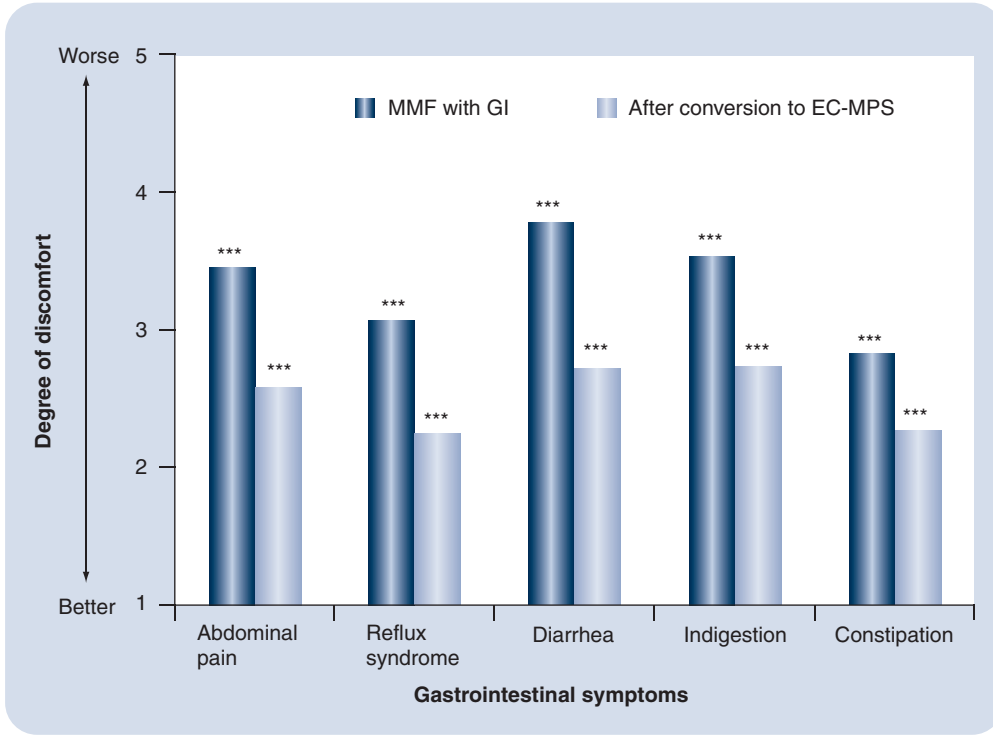
- Renal function was maintained over the course of the 6-month study, with no reports of graft loss or death
- Therapeutic doses of EC-MPS, CsA and steroids remained stable throughout the study
- The incidence of serious infections and malignancies was as expected and consistent with previous studies on EC-MPS
- Low incidence of dose reductions due to side effects – dose reductions following an AE occurred in 6.6% of patients
- No dose reductions following GI AEs

Independently from the above-mentioned studies, there are several reports of resolution of severe MMF-related GI AEs following conversion to EC-MPS [64].

Two recent studies, even if with discordant results, did afford the issue of GI side effects after conversion from MMF to EC-MPS. The objective of the first study was to evaluate the impact of GI complaints on symptom severity and health-related quality of life (HRQoL) in kidney transplant recipients and to determine if GI symptom severity and HRQoL improved after patients with GI complaints are converted from MMF to EC-MPS [65]. The study was an open-label, nonrandomized, international, longitudinal, observational trial. Patients were divided into two groups:

- Patients with GI complaints on MMF who were converted to equimolar doses of EC-MPS

Figure 7. GSRS scale comparison before and after conversion to EC-MPS.



Data presented at 3rd World Congress of Nephrology, Singapore, 2005.
EC-MPS: Enteric-coated mycophenolate sodium; GSRS: Gastrointestinal Symptoms Rating Scale; MMF: Mycophenolate mofetil. ***p < 0.001.

- Patients without complaints on MMF who remained on MMF throughout the study

Symptom severity and HRQoL were assessed with patient-reported questionnaires previously validated in the renal transplant population. These questionnaires were selected specifically to capture the impact of GI complaints rather than general renal transplant issues. The questionaires included:

- GI Symptoms Rating Scales (GSRS): a 15-item instrument to assess the degree of discomfort associated with symptoms of common disorders
- GI Quality of Life Index (GIQLI): a 36-item questionnaire to assess the impact of GI disease on daily life
- The Psychological General WellBeing Index (PGWB): a 22-item questionnaire to assess self representations of interpersonal affective or emotional states reflecting a sense of subjective wellbeing or distress

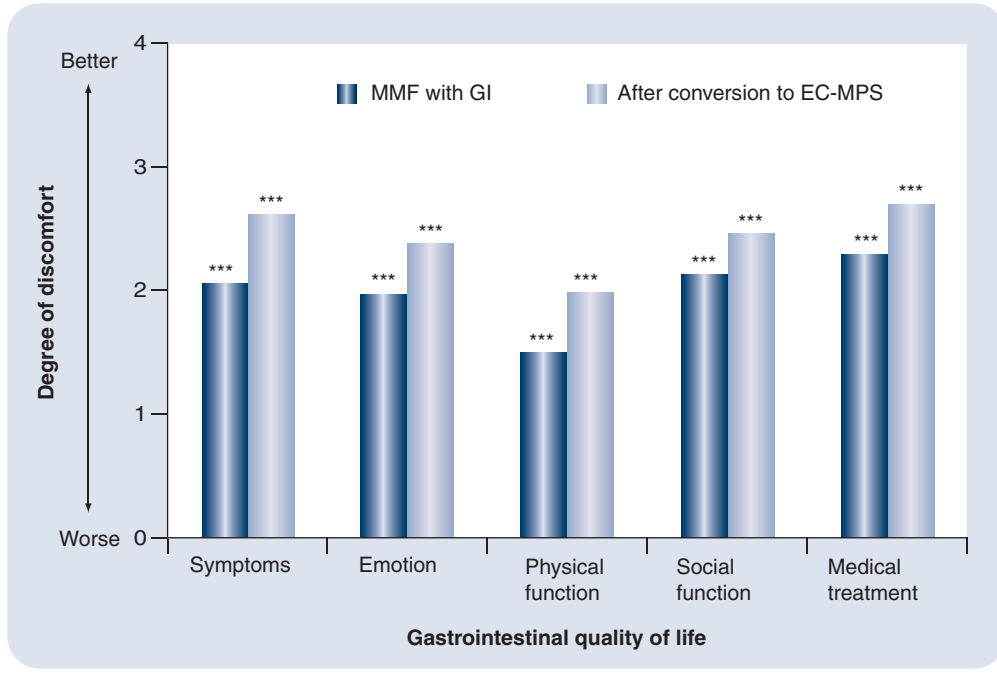
Figure 7 shows the GSRS scale comparison before and after conversion to EC-MPS. **Figure 8** shows the GIQLI scale comparison before and after conversion to EC-MPS.

This study provided the first evidence that GI complaints in renal transplant patients are associated with impairments in patient functioning in physical, social and psychological domains (HRQoL). The conversion of patients with GI complaints to an EC-MPS appears to significantly reduce GI symptom burden, to improve GI-specific HRQoL, and to improve general psychological wellbeing and HRQoL. One of the main limit of this study is that was not conducted as a crossover. Hence patients on EC-MPS were not again reconverted to MMF to further prove the efficacy of the EC.

Conversely, in another recently published study based on GI symptoms captured by questionnaires comparing patients on MMF with respect to patients on EC-MPS, GI tolerance of both regimens was similar in *de novo* renal transplant patients during the first year post-transplantation [66].

A large prospective, open-label, multicenter program (myPROMS: myfortic PROspective Multicenter Study) was conducted in order to determine the efficacy and safety of EC-MPS, in combination with CsA-ME in a large population

Figure 8. GIQLI score changes before and after conversion to EC-MPS



Data presented at 3rd World Congress of Nephrology, Singapore, (2005).
EC-MPS: Enteric-coated mycophenolate sodium; GIQLI: Gastrointestinal quality of life index; MMF: Mycophenolate mofetil. ***p < 0.001.

of *de novo* and maintenance renal transplant recipients. MyPROMS consisted of one global protocol with 14 subprotocols in specific patient populations, with different corticosteroid regimens, or with CsA administered according to different levels 2 h postdose (C2).

Nashan recently reported data from 226 patients treated by EC-MPS, CsA, with or without steroids, who switched from MMF to EC-MPS [67]. His data are in line with those of Budde and colleagues and confirm that renal transplant patients receiving MMF can be converted to EC-MPS with no compromise in efficacy and tolerability.

The safety and tolerability of converting patients from MMF to EC-MPS was also confirmed by two studies of a multicenter Latin American Study (LatAm) [68,69]. The study has been designed to enlarge the experience with EC-MPS in different ethnic groups. The authors conclude that EC-MPS is a valid alternative to MMF in maintenance renal transplant patients, possibly helping to minimize the risk of GI AEs and dose changes.

Two other studies from the myPROMS group documented the safety and efficacy of EC-MPS in *de novo* renal transplant recipients. Legendre reported the data at 1 year of 197 patients who received as primary immunosuppression basiliximab, EC-MPS, CsA-ME and steroids [70]. The conclusion of the study were that the incidence of EC-MPS dose reduction or interruption related to GI side effects was low. Dose reductions and interruptions were mainly related to common hematological AEs. Similar results were reported in a study from Vitko and colleagues on 140 patients receiving EC-MPS and CsA [71].

Vathsala reporting the data pooled in a planned analysis of three subprotocols of similar design from an international, prospective, open-label, multicenter study, carried out in Asia, Europe and Latin America [72]. The objective of the analysis were primarily to assess the efficacy and safety of the conversion from MMF to EC-MPS in a large population of maintenance renal transplant recipients. As a secondary objective, the study evaluated the use of PPIs and histamine-2 (H2) receptor blockers on the incidence of EC-MPS GI AEs and dose adjustments or temporary interruptions. The study concluded that EC-MPS was well tolerated in maintenance renal transplant recipients. The incidence of EC-MPS dose adjustments or temporary interruptions related to GI side effects were low, despite

Table 2. Incidence of patient and graft survival, BPAR and DGF according CsA levels.

Outcome	Delay CsA	Low C2	Mid C2	High C2
n	100	95	90	105
Patient survival (%)	99	98	100	99
Graft survival (%)	97	97	100	100
DGF (%)	29	17	13	13
BPAR (%)	30	21	24	22
CrCL (12 months)	59 ± 16	59 ± 18	58 ± 18	61 ± 17

BPAR: Biopsy-proven acute rejection; C2: 2 h postdose CsA level; CrCL: Creatinine clearance; CsA: Cyclosporin A; DGF: Delayed graft function. Data from Am. J. Transplant. *5 (S11), 464 (2005) [74].*

the high proportion (65.8%) of patients who were not receiving PPIs or H2 blockers and that EC-MPS is a safe and effective alternative to MMF in renal transplant recipients.

To assess the use of CsA in patients receiving EC-MPS, Mourad compared in 197 patients the use of early versus delayed introduction of CsA [73]. Renal function was not statistically different between the two groups at 12 months. Over 12 months the evidence of treatment failure and biopsy-proven acute rejection were not statistically different: 24.7 versus 27% and 18.6 versus 24% between the two groups.

Budde and colleagues used pooled data from three studies conducted within the myPROMS program in *de novo* kidney recipients, to compare the efficacy and tolerability of different exposures to CsA at day 5 post-transplantation in patients treated with basiliximab (SIM) and EC-MPS [74]. The results of these unpublished data are shown in **Table 2**. The author concluded that in a peritransplant regimen including SIM and EC-MPS, good efficacy is not significantly affected by the level of CsA exposure on day 5 and no significant change in incidence of delayed graft function and BPAR was observed with delayed introduction of CsA-ME.

Use of EC-MPS in nonkidney transplants

Although MMF has been used in liver and heart transplantation since the mid 1990s, only a few recent reports document the use of EC-MPS in nonkidney organ recipients.

Villamil switched from MMF to EC-MPS 17 liver transplant recipients who developed severe GI intolerance to MMF and required drug discontinuation [75]. After a follow-up period of 6 months, 12 of 17 patients recovered. In five of the patients the GI side effects persisted and four discontinued EC-MPS.

The CERL080A2401 heart study was designed to assess the safety and efficacy of EC-MPS in heart transplantation with respect to MMF. A total of 154 *de novo* heart transplant recipients were randomized to either EC-MPS or MMF [76]. The rate of treatment failure at 12 months was comparable in the two treatment groups. Significantly more patients on MMF had two or more dose reductions (42.1 vs 26.9%, p = 0.048). In conclusion, EC-MPS showed similar efficacy and safety results as MMF in *de novo* heart transplant recipients at 12 months. In a pharmacokinetic substudy comparing pharmacokineics of MMF with EC-MPS in heart transplant, it was shown that EC-MPS delivers efficacious, systemic MPA exposure [77]. The exposure to MPA and MPAG was similar after treatment with EC-MPS or MMF in the heart recipient population.

Expert commentary

In conclusion, EC-MPS has been proven to have similar efficacy to MMF, both in *de novo* kidney transplant patients and patients converted from MMF to EC-MPS. A similar safety profile has also been documented. In addition, EC-MPS and MMF have demonstrated similar efficacy and safety in heart transplant patients. Some very recent data demonstrate the benefit on GI symptoms and QoL conversion to EC-MPS mycophenolate sodium in patients receiving MMF who experienced GI side effects.

Outlook

Both T and B lymphocytes play a central role in the pathogenesis of rejection of transplanted organs. Calcineurin inhibitors (CNI) are now the cornerstone therapy in the prevention of rejection. Their main unwanted side effects on kidney function and metabolism appear to be mitigated as a result of the association of other agents as the antiproliferative. Such drugs indeed allow a reduction

in CNI dose. As a result, antiproliferative agents with a selective mechanism of action, such as MPA, are a relevant tool among other immunosuppressive agents in the prevention, control and treatment of rejection. As inhibitors of pyrimidine synthesis do not seem to maintain the expectancies, mainly due to relevant side effects, selective inhibitors of IMPDH will presumably play an important role in the forthcoming years.

EC-MPS has been documented in main registration studies as being as safe and effective as MMF. Ongoing worldwide studies are documenting an improved safety profile with reduced unwanted GI side effects.

Highlights

- Mycophenolic acid (MPA) has a pleiotropic mechanism of action: besides inhibition of lymphocyte proliferation, several studies document an action on adhesion molecules, macrophages and endothelium.
- Mycophenolate mofetil (MMF) has been successfully evaluated for the prevention of acute allograft rejection in three randomized, double-blind, multicenter trials involving almost 1500 adult renal transplant patients.
- Notwithstanding, the relatively high incidence of gastrointestinal (GI) side effects reported in patients receiving MMF may limit its efficacy due to the necessity of dose reduction.
- An enteric-coated mycophenolate sodium (EC-MPS) was developed to improve MPA-related upper GI adverse events.
- Several clinical pharmacology studies have been conducted, which established that 720 mg of sodium MPA was equivalent to 1000 mg of MMF in terms of exposure.
- Two double-blind, placebo-controlled studies have been conducted and were the basis for the registration of EC-MPS in Europe and the USA. Both studies established a similar efficacy and safety profile for MMF and EC-MPS.
- A large, prospective, open-label, multicenter program (myfortic PROspective Multi-center Study [myPROMS]) was conducted to determine the efficacy and safety of EC-MPS, in combination with cyclosporin microemulsion in a large population of *de novo* and maintenance renal transplant recipients. Overall, the myPROMS studies confirm the safety and efficacy of EC-MPS in different populations and in different immunosuppressant associations.

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