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Enteric-Coated Mycophenolate Sodium

Tolerability Profile Compared with Mycophenolate Mofetil

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Abstract

Mycophenolate mofetil is one of the most frequently used immunosuppressive drugs in solid organ transplantation. Although the adverse effect profile of mycophenolate mofetil is comparatively benign, gastrointestinal adverse effects are a major concern. The adverse effects may require a dose reduction or discontinuation, thus limiting its clinical efficacy. Enteric-coated (EC) mycophenolate sodium is a new formulation of mycophenolic acid (MPA) that delivers the active moiety MPA, the same active moiety delivered by mycophenolate mofetil. It has been developed to help protect the upper gastrointestinal tract. It is implied that a reduction of adverse drug effects as well as a reduction of dose may improve efficacy and compliance. Noncompliance is often underestimated in solid organ transplant recipients, and adverse drug effects increase medication nonadherence. Recent clinical trials comparing EC mycophenolate sodium and mycophenolate mofetil in kidney recipients reported similar rates of efficacy and adverse effects. It is noteworthy that systemic MPA exposure is higher with EC mycophenolate sodium than with mycophenolate mofetil, without increased gastrointestinal toxicity. This finding is quite surprising, because part of MPA-associated gastrointestinal toxicity is related to its antiproliferative effect on enterocytes. However, enteric coating of MPA did not markedly reduce the number of gastrointestinal adverse effects. Further studies focusing on dosage, therapeutic drug monitoring and immunosuppressive regimens may reveal benefits of EC mycophenolate sodium for optimal individualised immunosuppression and improved compliance. At present, EC mycophenolate sodium is an alternative immunosuppressant to mycophenolate mofetil in kidney transplant recipients with an almost identical efficacy and safety profile.

The introduction of mycophenolate mofetil has resulted in a significant and clinically important step forward in improving the outcome of kidney transplantation.[1] Mycophenolate mofetil, in combination with a calcineurin inhibitor and corticosteroids was superior to placebo or azathioprine in preventing acute rejection.[2-6] A further advantage of mycophenolate mofetil is the lack of neuro- and nephrotoxicity.[7,8] The proportion of patients receiving mycophenolate mofetil has increased from

11% in 1995 to 77% in 1999, as analysed by the United Network for Organ Sharing (UNOS) renal transplant registry.[9] However, the use of mycophenolate mofetil is associated with a number of gastrointestinal adverse effects (e.g. diarrhoea), cytopenias (e.g. leukocytopenia) and opportunistic infections (e.g. cytomegalovirus). To avoid drug toxicity or concurrent infection recipients commonly respond to dose reduction, discontinuation or withdrawal of mycophenolate mofetil, but this may increase the incidence of rejection and reduce graft survival.[10] For this reason, enteric-coated (EC) mycophenolate sodium was designed to reduce the incidence of gastrointestinal symptoms reported with mycophenolate mofetil.[11,12]

Generic substitution of pharmaceuticals is commonplace in healthcare. The US FDA has incorporated guidelines for drugs to be considered as bioequivalent.[13,14] For example, the differences in mean area under the plasma concentration-time curve (AUC) must be within the range of −20% to +25%. However, small changes in systemic concentrations of narrow-therapeutic index drugs can lead to great differences in pharmacodynamic response. Bioequivalent azathioprine products may produce different effects on thiopurine S-methyltransferase (TPMT) activity, especially in the case of TPMT-deficient individuals, which has not yet been evaluated.[13] Generic narrow-therapeutic-index immunosuppressive agents provide adequate *de novo* immunosuppression in low-risk transplant recipients; however, concerns exist regarding the unquantified risk that may be associated with switching immunosuppressive agents under uncontrolled circumstances.[15]

The generic replacement of an immunosuppressive drug requires the patient's compliance. Adverse drug effects, particularly diarrhoea, may reduce compliance by increased drug nonadherence. Compliance is an important and often underestimated issue with respect to transplant recipients. The selection of immunosuppression protocols that involve fewer adverse effects and fewer medications can help to increase patient satisfaction, improve compliance, maintain graft function and enrich the long-term quality of life of transplant recipients.[16] The potential effect of EC mycophenolate sodium on compliance is the subject of further discussion.

1. Description of Enteric-Coated (EC) Mycophenolate Sodium

1.1 Drug Chemistry

In contrast to mycophenolate mofetil, the semisynthetic morpholinoethyl ester of mycophenolic acid (MPA), EC mycophenolate sodium contains MPA in its active form.[17] The mofetil group is replaced by sodium (figure 1). EC mycophenolate sodium has the chemical formula $C_{17}H_{19}NaO_6$ and is a sodium 4(E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,2-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate with a molecular weight of 342.32.[12]

1.2 Mode of Action

The active compound of EC mycophenolate sodium is MPA, a noncompetitive reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a key enzyme in *de novo* purine synthesis. Its inhibiting properties block lymphocyte proliferation in the S-phase. There are two isoforms of IMPDH: IMPDH type I is mainly located in nonproliferating cells, whereas type II is the predominant isoform in lymphocytes, and nearly 5-fold more sensitive to inhibition by MPA than type I.[18-20] Other cell types that use the IMPDH-independent salvage pathway for regeneration of their purine pool are not consid-

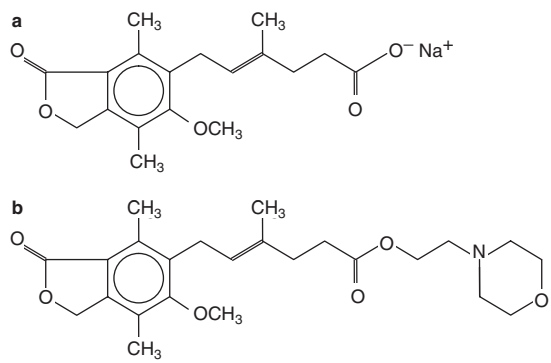

Fig. 1. Molecular structure of (**a**) mycophenolate sodium and (**b**) mycophenolate mofetil.

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Table I. Comparison of mean (± SD) pharmacokinetic and pharmacodynamic parameters in 14 kidney recipients receiving enteric-coated mycophenolate sodium (EC MPS) 720mg twice daily or mycophenolate mofetil (MMF) 1000mg twice daily[28]

Parameter	EC MPS	MMF
MPA C_{max} (ng/mL)	19.2 ± 8.9	20.2 ± 8.6
MPA AUC (μg • h/mL)	56.0 ± 15.3	55.7 ± 9.9
MPA t_{max} (h)	2.3 ± 1.4*	0.9 ± 0.4
MPA trough levels (ng/mL)	3.65 ± 2.29	1.57 ± 0.65
Predose IMPDH activity (nmol/h/mg)	5.4 ± 1.9*	9.8 ± 3.5
Lowest daytime IMPDH activity (nmol/h/mg)	1.4 ± 0.9	1.6 ± 1.5
IMPDH inhibition (%)	72.0 ± 19.0	84.0 ± 12.0
Daytime average IMPDH activity (nmol/h/mg)	4.9 ± 1.2	5.8 ± 1.9

AUC = area under the plasma concentration-time curve; **C_{max}** = peak plasma concentration; **IMPDH** = inosine monophosphate dehydrogenase; **MPA** = mycophenolic acid; **t_{max}** = time to C_{max}; * p = 0.01 vs MMF.

erably affected by MPA, except enterocytes, which are approximately 50% IMPDH-dependent.[21-23] The depletion of guanosine nucleotides by MPA influences DNA synthesis and also glycosylation of adhesion molecules. Thereby, MPA blocks proliferation and clonal expansion in T and B lymphocytes, inhibits antibody production and prevents the generation of cytotoxic T cells.[17,18,22,24]

1.3 Dosage, Application and Metabolism

EC mycophenolate sodium is administered orally in two fixed doses per day, exactly as mycophenolate mofetil. EC mycophenolate sodium is available in the form of 180 and 360mg tablets, and these are approximately one-third smaller than standard mycophenolate mofetil tablets.[11] The tablets should not be crushed before oral intake, in order to preserve the enteric coating,[25] which allows passage of the undissolved tablets into the small bowel. EC mycophenolate sodium is maximally released at pH 6.0–6.8 after 120 minutes.[11] In contrast, mycophenolate mofetil is rapidly absorbed in the stomach.[12] Mycophenolate mofetil and EC mycophenolate sodium are contraindicated during pregnancy and in breast-feeding women because of teratogenic effects proven in animal experiments. Preliminary data on humans also exist.[26] Thus, mycophenolate mofetil and EC mycophenolate sodium should be administered to women only if they have a negative pregnancy test and are using effective contraception 6 weeks before, during and after administration.[25]

MPA AUC and 7-*O*-MPA-β-glucuronide (MPAG) AUC of EC mycophenolate sodium 720mg are bioequivalent to that of mycophenolate mofetil 1000mg.[27] EC mycophenolate sodium and mycophenolate mofetil dosages revealed identical drug exposure, minor pharmacokinetic differences, and similar pharmacodynamic response (table I).[28] After kidney transplantation, the MPA peak plasma concentration (C_{max}) and AUC (ranging from 5.0 to 40 μg • h/mL) increased proportionally with doses.[29,30]

The mean absolute bioavailability of MPA after oral application is >71%, and the steady-state volume of distribution is 50L.[12,31] MPA is metabolised mainly by hepatic uridine diphosphate-glucuronyltransferases (UGTs) to MPAG, which undergoes enterohepatic recirculation.[32] Hepatic dysfunction can lead to impaired glucuronidation of mycophenolate mofetil.[32] MPA and MPAG are highly albumin bound, by 97% and 82%, respectively. The mean half-life of MPA and MPAG is 11.7 and 15.7 hours, respectively.[12,31] Recently, further metabolites have been detected (table II).[33-35] Gut bacteria glucuronidases reconvert MPAG to MPA, which is

Table II. Overview of mycophenolic acid (MPA) metabolites[1,33]

Abbreviation	Metabolite	Comments
MPA	Mycophenolic acid	Pharmacologically active compound
MPAG	7-*O*-mycophenolic acid-β-glucuronide	Inactive main metabolite of MPA, pharmacological activity is under discussion
M-1	7-hydroxy-glucose conjugate of MPA	
M-2	Acyl glucuronide conjugate of MPA	Pharmacologically active metabolite, toxic potential, interacts with enzyme-multiplied immunoassay technique
M-3	Not further described	Detected after incubation of human liver microsomes

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reabsorbed and recirculated. More than 90% of orally administered mycophenolate mofetil is eliminated in the urine as MPAG.[31,32] Impaired kidney function can lead to high MPAG concentrations and may increase the free MPA fraction from competition at the albumin-binding sites.[36] This effect is potentiated in the presence of hypoalbuminaemia.[37] Further detailed information regarding MPA pharmacokinetics are described elsewhere.[1,22,31,32,38-41]

1.4 Drug Interactions

Potential aspects of EC mycophenolate sodium drug interactions are absorption, albumin binding, metabolism by UGT, bile flow and urinary excretion. The concomitant administration of EC mycophenolate sodium and magnesium- or aluminium-containing antacids, ferrous sulfate or polycarbophil calcium reduces absorption,[12,42,43] while colestyramine, antibacterials (e.g. fluoroquinolones) and selective bowel decontamination reduce absorption and enterohepatic recirculation.[12,44,45] Also, maintenance immunosuppression with ciclosporin and EC mycophenolate sodium resulted in reduced absolute bioavailability of MPA.[12] Inhibitors of tubular secretion (e.g. aciclovir, probenecid) may increase the concentration of MPAG.[12,45] EC mycophenolate sodium and mycophenolate mofetil share the same active compound. Thus, it is predicted that drug interactions reported for mycophenolate mofetil may also occur in EC mycophenolate sodium-treated transplant recipients (table III).[45-51]

1.5 Therapeutic Drug Monitoring

MPA plasma concentrations can be measured by reverse phase high-performance liquid chromatography (RP-HPLC) or enzyme-multiplied immunoassay technique.[41,52,53] The value of therapeutic drug monitoring is a subject of controversial discussion.[54-56] Recently, upper and lower limits of a target therapeutic range of MPA trough levels (1.5–3 mg/L) and MPA AUC (30–60 mg • h/L) have been suggested in mycophenolate mofetil-treated

Table III. Drug interactions of mycophenolic acid (MPA) prodrugs enteric-coated mycophenolate sodium (EC MPS) and mycophenolate mofetil[12,42-51]

Drug	Suggested mechanism	Comments
Absorption interactions		
Magnesium/aluminium-containing antacids	Inhibition of absorption in gastrointestinal tract	Coadministration of these antacids decreased MPA AUC by 25–37%
Polycarbophil calcium	Decreased absorption	
Metabolism interactions		
Ciclosporin, tacrolimus	Ciclosporin inhibits MPAG excretion into bile; tacrolimus potentially affects glucuronidation	Ciclosporin /EC MPS comedication decreased MPA AUC by 20–30%. Higher MPA trough levels in combination with tacrolimus than with ciclosporin
Corticosteroids	Induction of UGT	Corticosteroid withdrawal results in increase of MPA trough levels and MPA AUC
Enterohepatic recirculation		
Colestyramine, bile acid-binding agents	Inhibition of enterohepatic recirculation of MPA	Reduced bioavailability of MPA
Selective bowel decontamination	Interruption of enterohepatic recirculation	Selective bowel decontamination decreases mean MPA bioavailability by 7–54%
Renal excretion		
Aciclovir, ganciclovir	Competitive inhibition of tubular secretion	Increase of MPAG and/or aciclovir/ganciclovir blood levels, especially in patients with impaired renal function
Other interactions		
Attenuated live vaccination	Immunosuppression	Active live vaccination should be avoided under immunosuppressive state; other vaccinations may result in impaired response

AUC = area under the plasma concentration-time curve; **MPAG** = 7-*O*-mycophenolic acid-β-glucuronide; **UGT** = uridine diphosphate glucuronyltransferase.

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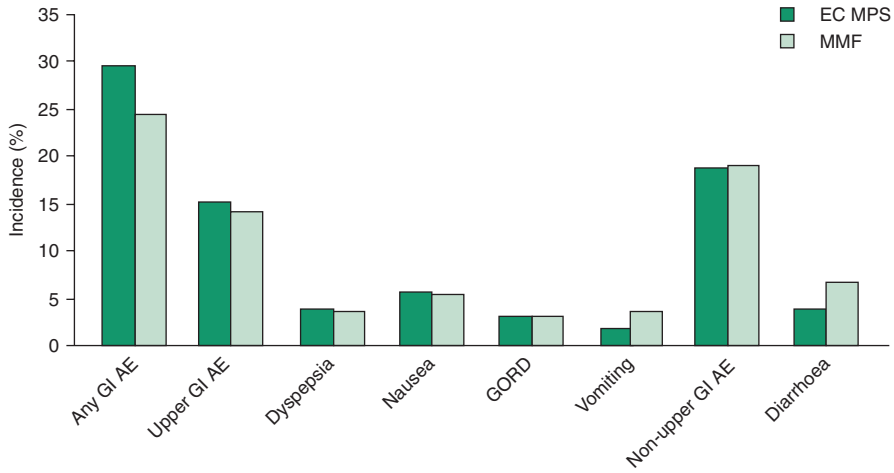

Fig. 2. Incidence of gastrointestinal (GI) adverse events (AEs) with enteric-coated mycophenolate sodium (EC MPS) and mycophenolate mofetil (MMF) at 12 months in the ERL B302 study.[61] **GORD** = gastro-oesophageal reflux disease.

kidney transplant recipients.[54,57] However, MPA predose plasma levels have high interindividual variability under a fixed mycophenolate mofetil dose.[58] Monitoring of abbreviated MPA AUCs is one favoured strategy to improve the therapeutic drug monitoring of mycophenolate mofetil,[40,41,55,56] but the delayed time to C_{max} (t_{max}) of EC mycophenolate sodium has to be taken into consideration with this approach. Nevertheless, MPA plasma concentration monitoring is an objective method of verifying compliance.

2. Preclinical Studies

In rodent transplantation models, minimal efficacious doses of mycophenolate sodium were related to first signs of adverse effects, indicating a narrow therapeutic window. There was no potential synergy between ciclosporin and mycophenolate sodium or mycophenolate mofetil in respect to the efficacy, but fewer adverse effects were noted in combination with mycophenolate sodium. Monotherapy of mycophenolate sodium was better tolerated than mycophenolate mofetil in some of the transplant models.[59]

Mycophenolate mofetil and EC mycophenolate sodium were investigated in beagle dogs (n = 4 per group). All placebo-treated dogs appeared healthy, whereas 75% of mycophenolate mofetil- and 100% of EC-mycophenolate sodium-treated dogs developed gastrointestinal adverse effects. Histologically, animals with diarrhoea had enteritis and colitis with scattered foci of cryptitis and/or crypt abscesses. MPA AUC_{12h} 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 diarrhoea nor avoided intestinal mucosa abnormalities, as seen with mycophenolate mofetil.[60]

3. Clinical Studies

3.1 Comparing Adverse Events, Safety and Efficacy of Conversion

The incidence of EC mycophenolate sodium- and mycophenolate mofetil-induced gastrointestinal adverse events and neutropenia at 3 months was compared in a phase III randomised, double-blind, double-dummy, multicentre trial in adult kidney recipients.[61] Concomitant immunosuppression consisted of ciclosporin microemulsion and corticosteroids. Stable patients were randomised to mycophenolate mofetil, EC mycophenolate sodium or placebo, at least 6 months after transplantation. During the study, 10.1% of EC mycophenolate sodium-treated patients and 11.7% of mycophenolate mofetil-treated patients discontinued treatment prematurely. Ad-

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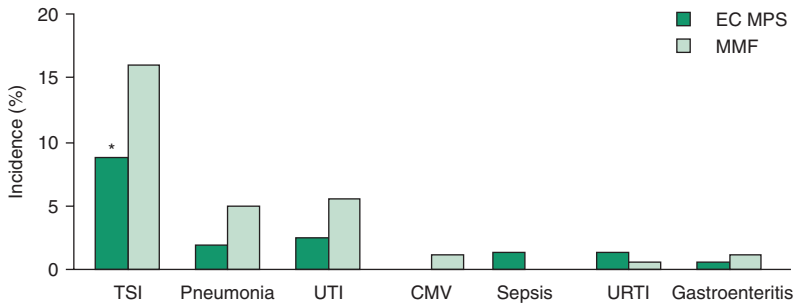

Fig. 3. Incidences of infectious adverse events at 12 months in the ERL B302 study.[61] **CMV** = cytomegalovirus including CMV infection and pneumonia; **EC MPS** = enteric-coated mycophenolate sodium; **MMF** = mycophenolate mofetil; **TSI** = total serious infection; **URTI** = upper respiratory tract infection; **UTI** = urinary tract infection including pyelonephritis and urosepsis; * $p < 0.05$.

verse events were the reason for discontinuation in 5.7% of patients in the EC mycophenolate sodium and 2.5% in the mycophenolate mofetil group. The incidence of gastrointestinal adverse events was similar at 3 months (EC mycophenolate sodium group 26.4% vs mycophenolate mofetil group 20.9%; p = not significant [NS]) and at 12 months (29.6% vs 24.5%; p = NS) [figure 2]. However, the increase from baseline in the gastrointestinal adverse event severity score, adjusted for duration, tended to be lower in the EC mycophenolate sodium group at 3 months (0.15% vs 0.20%; p = NS) and at 12 months (0.23% vs 0.47%; p = NS). The incidence of neutropenia at 3 months was low in both groups (0.6% vs 3.1%; p = NS). The rates of efficacy failure (2.5% vs 6.1%; p = NS), biopsy-proven acute rejection (1.3% vs 3.1%; p = NS) and biopsy-proven chronic rejection (3.8% vs 4.9%; p = NS) were similar. Interestingly, the number of serious infections was significantly lower in EC mycophenolate sodium-treated patients (8.8% vs 16.0%; $p < 0.05$) [figure 3]. The changeover from mycophenolate mofetil to EC mycophenolate sodium during maintenance immunosuppression appeared to be safe and effective after kidney transplantation.[61]

3.2 Demonstration of Therapeutic Equivalence and Comparison of Safety Profile

In a phase III 12-month, international, randomised, double-blind, parallel-group study, the therapeutic equivalence of EC mycophenolate sodium 720mg twice daily (n = 213) to mycophenolate mofetil 1000mg twice daily (n = 210) was investigated in 423 *de novo* renal transplant recipients.[62] Concomitant immunosuppression consisted of ciclosporin microemulsion and corticosteroids. Additional induction with antilymphocyte globulin, antithymocyte globulin, muromonab CD3 (OKT3) or anti-interleukin-2 monoclonal antibody was allowed. At 12 months, the incidence of efficacy failure, defined as biopsy-proven acute rejection, graft loss or death was 26.3% in the EC mycophenolate sodium and 28.1% in the mycophenolate mofetil group (p = NS), and adverse events were similar at 12 months (figure 4). There was a trend towards fewer severe rejection episodes and dose changes due to gastrointestinal adverse events in the EC mycophenolate sodium group, without reaching statistical significance (table IV).[62]

3.3 Clinical Pharmacokinetics in *de Novo* Kidney Recipients

In a subgroup analysis of a multicentre trial (ERL B301), MPA pharmacokinetics were measured by HPLC on days 14, 90 and 180 after transplant in kidney recipients, 27 receiving EC mycophenolate sodium 720mg twice daily and 28 receiving mycophenolate mofetil 1000mg twice daily.[30] The mean systemic MPA exposure increased by 60–90% over a period of 6 months with both EC mycophenolate sodium and mycophenolate mofetil. The mean systemic MPA exposure (μg • h/mL) of EC mycophenolate sodium versus mycophenolate

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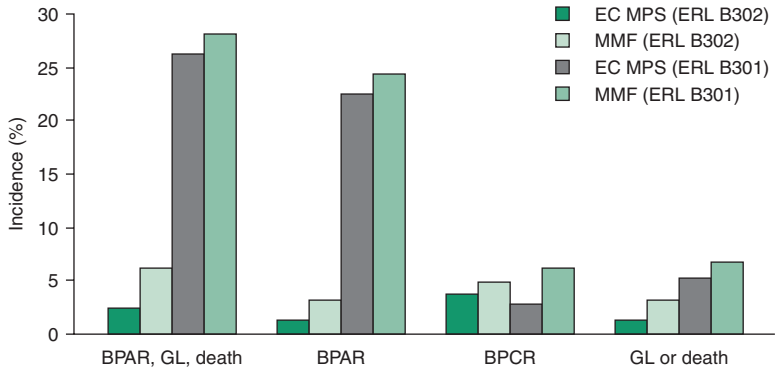

Fig. 4. Efficacy of enteric-coated mycophenolate sodium (EC MPS) and mycophenolate mofetil (MMF) at 12 months in the ERL B302 and ERL B301 study.[61,62] **BPAR** = biopsy-proven acute rejection; **BPCR** = biopsy-proven chronic rejection; **GL** = graft loss.

mofetil was 29.1 versus 23.3 on day 14, 50.7 versus 39.1 on day 90 and 55.7 versus 37.2 on day 180. The corresponding MPA C_{max} (μg/mL) was 13.9 versus 11.6 on day 14, 24.6 versus 17.9 on day 90 and 23.0 versus 18.6 on day 180. The mean systemic MPA exposure increase associated with EC mycophenolate sodium relative to mycophenolate mofetil was 32%. A higher percentage of patients in the EC mycophenolate sodium group reached a mean systemic MPA exposure above 30 μg • h/mL, which is suggested for the prevention of acute rejection in kidney recipients (figure 5).[30]

3.4 Myfortic Prospective Multicenter Study

At present, the efficacy and safety of EC mycophenolate sodium are being evaluated by an ongoing prospective, open-label, multicentre, international study (myPROMS [Myfortic Prospective Multicenter Study]).[63] Approximately 1800 *de novo* kidney recipients have been assigned to par-

Table IV. 1-Year results of two phase III multicentre studies (ERL B301 and ERL B302) comparing enteric-coated mycophenolate sodium (EC MPS) and mycophenolate mofetil (MMF) after kidney transplantation[61,62]

Parameter	ERL B301		ERL B302	
	EC MPS	MMF	EC MPS	MMF
No. of patients	213	210	159	163
Graft loss or death (%)	5.2	6.7	1.3	3.1
Efficacy failure[a] (%)	28.6	28.1	7.5	12.3
Biopsy-proven acute rejection (%)	22.5	24.3	1.3	3.1
Biopsy-proven chronic rejection (%)	2.8	6.2	3.8	4.9
Any AEs (%)	98.1	98.1	93.7	92.6
Serious AE (%)	54.9	53.8	23.3	30.1
Any infection (%)	69.5	73.3	58.5	58.9
Serious infection (%)	22.1	27.1	8.8*	16.0
Pneumonia (%)	0.5**	4.3	1.9	4.9
CMV infection (%), CMV disease (%)	21.6, 4.7	20.5, 4.3	1.9, 0	1.8, 0.6
Neutropenia [<1500/mm^3] (%)	0.9	3.3	0.6	3.1
GI AE (%)	80.8	80.0	29.6	24.5
Upper GI AE (%), non-upper GI AE (%)	53.5, 68.5	54.3, 68.1	15.1, 18.9	14.1, 19.0
Study drug discontinued (%)	20.2	18.6	10.1	11.7
Dose changes due to GI AE (%)	15.0	19.5	5.0	4.3

a Defined as biopsy-proven acute rejection, graft loss, death or loss to follow-up.

AE = adverse event; **CMV** = cytomegalovirus; **GI** = gastrointestinal; * $p < 0.05$, ** $p = 0.01$ vs MMF.

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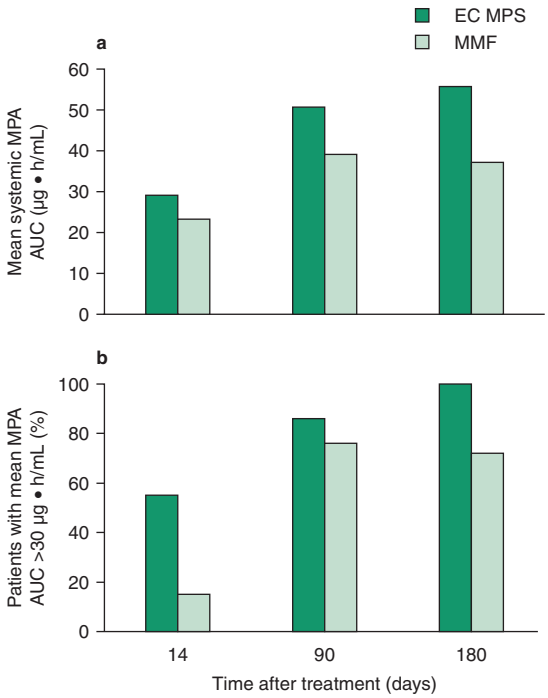

Fig. 5. Comparison of mean systemic mycophenolic acid (MPA) area under the plasma concentration-time curve (AUC) at days 14, 90 and 180 after administration of enteric-coated mycophenolate sodium (EC MPS) 720mg twice daily (n = 27) or mycophenolate mofetil 1000mg twice daily (n = 28) in kidney recipients (**a**), and percentage of patients with mean MPA AUC >30 µg • h/mL (**b**).

ticipate. Fourteen subprotocols aim at specific objectives, such as corticosteroid regimens, ciclosporin 2-hour postdose (C2)-monitoring and others. Two subprotocols (DE02 and LA01) focus on converting maintenance kidney recipients from mycophenolate mofetil to EC mycophenolate sodium. In the DE02 study, mycophenolate mofetil was switched to the bioequivalent EC mycophenolate sodium dose. At 3 months, there was no death, graft loss or chronic rejection.[63]

A recently published interim analysis reported 3-month results after conversion from mycophenolate mofetil 2 g/day to EC mycophenolate sodium 1.44 g/day (0.450 g/m^2 in children) in 93 patients.[64] After conversion, the total incidence of adverse events was 40.9%, including infections (28%), haematological adverse events (1.1%), gastrointestinal symptoms (19.4%), mild upper gastrointestinal adverse events (10.8%) and diarrhoea (5.4%). None of the patients discontinued the study because of adverse events. EC mycophenolate sodium dosage adjustment was required in 6% of the patients. There were no episodes of acute rejection, death or graft loss. The investigators concluded that the conversion from mycophenolate mofetil to EC mycophenolate sodium prevented the release of MPA in the upper gastrointestinal tract and is as safe and effective as mycophenolate mofetil. It offers an alternative MPA therapy, but in a formulation that may provide gastrointestinal tolerability benefits.[64]

4. Compliance of Solid Organ Transplant Recipients

Noncompliance can be defined as covert nonadherence to prescribed medication used for the prophylaxis of allograft rejection and threatening impaired graft histology or function.[65] Life-long immunosuppression is a prerequisite for good graft function and outcome. Nonadherence to an immunosuppressive regimen can cause late acute rejection, graft loss and death. One might assume that transplant recipients constitute a highly motivated and compliant group, but unfortunately overall noncompliance rates reach up to 50%.[66-69] However, data on noncompliance, especially with newer immunosuppressive drugs, are rare and studies often fail to use standardised methods of assessing adherence.[70] Also, results from clinical studies may be better than in the normal clinical routine because of closer monitoring.

After kidney transplantation, incidence of medication noncompliance ranges from 15% to 52%.[71-75] Cluster analyses identified three distinct profiles of noncompliers: accidental noncompliers, invulnerables and decisive noncompliers.[72,76] The individual compliance of azathioprine in 180 renal transplant patients ranged from 16% to 100%. Declining compliance within the first 3 months after transplantation strongly increased the risk of late acute rejection and graft loss.[77] In a retrospective study, 91% of noncompliant recipients either lost their grafts or died.[71] Noncompliance is associated with a 3.2-fold higher risk and rate of acute late

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rejection and inferior 5-year graft survival.[73,74] Compliance in kidney recipients was higher for immunosuppressive than antihypertensive drugs. Noncompliance for prednisolone was higher in women than in men, and significantly associated with the rate of acute rejection.[78]

Compliance is even more important after life-saving solid organ transplantations, such as heart or liver transplantation. Heart transplant recipients with a median follow-up of 3 years revealed an overall medication compliance of 99.4%. The rate of late acute rejections increased with the grade of noncompliance.[79] However, noncompliance after heart and liver transplantation occurred even many years after transplant.[71]

Reported risk factors of noncompliance are adverse drug events, younger age, female sex, unmarried status of recipients, non-Caucasian race, being a living-donor transplant recipient, emotional problems (e.g. anxiety, hostility, depression), frequent dose administration, patient's perception of treatment benefits, poor patient-physician communication, lack of motivation, poor socioeconomic background, and lack of family and social support.[80-82] The costs of immunosuppression did not affect compliance.[75] Medication noncompliance is more than four times greater in adolescents than in adults.[83] Forgetfulness is cited as the main reason for nonadherence, but not adverse drug effects.[84] Preemptive kidney transplantation did not increase the rate of noncompliance.[85] Noncompliance to immunosuppressive drugs amounts to approximately 20%.[67] Adverse drug effects may decrease compliance, especially if they affect the quality of life during maintenance immunosuppression. Corticosteroids and calcineurin inhibitors increase the risk of hypertension, hyperlipidaemia, hyperglycaemia and osteopenia. Ciclosporin-associated hirsutism and gingival hyperplasia, corticosteroid-associated cushingoid features and obesity, and tacrolimus-induced alopecia are troublesome cosmetic adverse events that can reduce a patient's self-esteem and increase medication nonadherence.[81] The spectrum of immunosuppressive drug-related adverse effects is extended by rapamycin-associated hyperlipidaemia and mycophenolate mofetil-associated gastrointestinal toxicity, especially diarrhoea.

The detection of noncompliance can be difficult and may be initially indicated by deteriorated graft function. Frequent trough level monitoring of immunosuppressants with a narrow therapeutic index can be successfully utilised to identify recipients at risk for nonadherence to the immunosuppressant regimen.[84,86] Therapeutic drug monitoring may detect noncompliance at the earliest point in time, and trough level-adjusted administration might decrease noncompliance with the avoidance of under- and over-immunosuppression. Further approaches for diagnosis of noncompliance include the observation of behaviour with the aid of pill counting or electronic measurements of pill container opening, physical examination and observation of the consequences.[65]

5. Effect of EC Mycophenolate Sodium on Compliance in Transplant Recipients

It is difficult to predict the compliance of an individual transplant patient, especially during conversion or starting a new immunosuppressive drug. Acceptance of the 'new', as opposed to the 'well tried', requires potential benefits for the individual. EC mycophenolate sodium has revealed similar safety and efficacy results to mycophenolate mofetil in two randomised, double-blind, multicentre studies. The only significant differences were a reduced rate of pneumonia in the EC mycophenolate sodium group of the ERL B301 study and a lower rate of serious infections in the EC mycophenolate sodium group of the ERL B302 study.[61,62] The potential advantages of EC mycophenolate sodium over mycophenolate mofetil are the smaller size of the tablets, a higher percentage of kidney recipients reaching a systemic MPA exposure >30 μg • h/mL earlier without increased gastrointestinal toxicity, and a trend towards fewer dose changes in *de novo* kidney recipients. These potential advantages imply better control of dosage adjustment.

In a retrospective analysis, 507 of 721 (70.3%) mycophenolate mofetil-treated recipients received a dosage adjustment in the first year after kidney

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transplantation. Mycophenolate mofetil dose was reduced in 378 (52.4%) and discontinued in 102 (14.2%) patients. In a subanalysis of 322 patients undergoing 508 mycophenolate mofetil dose changes, 21% were due to gastrointestinal adverse effects such as diarrhoea, abdominal pain and intestinal bleeding. Mycophenolate mofetil dose changes significantly decreased 3-year graft survival (76.3% vs 88.3%; $p = 0.003$) and increased the risk of acute rejection (3.7% vs 23.3%; $p < 0.0001$) compared with no dose changes. Early dose reduction (0–30 days) was associated with the highest incidence (34.3%) of acute rejection.[10] This was confirmed by a retrospective study in 213 renal transplant recipients. The relative risk of rejection increased by 4% for each week that the mycophenolate mofetil was below 2 g/day.[87]

The results of the ERL B301 study suggest that the lower rate of dose changes as a result of gastrointestinal adverse events observed with EC mycophenolate sodium may be related to the enteric-coated formulation and may improve MPA gastrointestinal tolerability.[88] However, this hypothesis is not confirmed by the ERL B302 study. Gastrointestinal adverse events and related dose changes did not reach significant differences between EC mycophenolate sodium and mycophenolate mofetil in either study.[61,62] Therefore, post-transplant diarrhoea and MPA-related gastrointestinal disturbances are discussed briefly.

The pathophysiology of gastrointestinal intolerance seen with mycophenolate is still unclear and complex. Diarrhoea, nausea and vomiting are common post-transplant complications.[89,90] The aetiology includes surgery, infection and immunosuppressive drug-induced toxicity.[90] The incidence of diarrhoea and other gastrointestinal adverse effects reported at present for most clinical trials is at best unreliable, and at worst misleading. Moreover, the inappropriate dose reduction of an immunosuppressive agent that may not be the cause of diarrhoea may result in an unnecessary increase of rejection and graft loss.[91] Infection- and immunosuppression-related gastrointestinal disease can be distinguished by fever (>50% infection), inflammatory cells in stool (25–40% infection), abnormal endoscopy or computed tomography findings (≥50% infection) and leukocytosis (≥50% infection).[90]

Gastrointestinal symptoms, especially diarrhoea, are common adverse events during therapy with mycophenolate mofetil.[23] In the European and Tricontinental mycophenolate mofetil trials, the duration of diarrhoea increased from 6 months to 3 years in the mycophenolate mofetil and azathioprine groups, but was unchanged in the placebo group.[2,3,5,91] Also, incidences of diarrhoea differ according to the type of organ transplant and increase stepwise from renal to cardiac to liver transplantation.[91-93] Histologically, erosive enterocolitis was reported in kidney recipients and the development of bloody diarrhoea in patients with previously quiescent ulcerative colitis – both treated with mycophenolate mofetil.[94,95] Colonic biopsies of kidney recipients with mycophenolate mofetil-related diarrhoea revealed prominent crypt cell apoptosis and reactive or reparative changes, including enterocyte cytological atypia, increased neuroendocrine cells and glandular architectural distortion.[96]

Recently, an acyl metabolite of MPA (M-2) has been detected in transplant recipients.[97] M-2 induces proinflammatory cytokines *in vitro*.[98,99] Acyl glucuronides are reactive drug metabolites bearing a carboxylic acid function and they possess toxic potential, either by direct tissue damage or by the formation of adducts with proteins, but this has so far not been proven for M-2.[35,100]

Dose-dependent effects on the post-transplant diarrhoea rate have been shown for mycophenolate mofetil 2 versus 3 g/day and rapamycin 2 versus 5 mg/day.[2,3,5,101] Further investigations revealed half the incidence of diarrhoea in recipients with MPA AUC of 30 versus 60 μg • h/mL.[40] Also, a combination of immunosuppressive drugs can increase the incidence of gastrointestinal adverse effects, as reported in the case of tacrolimus and azathioprine or mycophenolate mofetil, as well as rapamycin and mycophenolate mofetil.[102,103] The route of administration does not necessarily affect the incidence of diarrhoea. A comparison of intravenous and oral mycophenolate mofetil application

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resulted in a modest increase of diarrhoea with the intravenous formulation, which might be explained by a higher MPA AUC. Therefore, gastrointestinal intolerance of mycophenolate mofetil was suggested to be a systemic and not a topical effect.[91] Furthermore, enterocytes are approximately 50% dependent on IMPDH.[23] Thus, MPA may affect enterocyte regeneration directly at the luminal surface as well as systemically. The direct influence, especially in the upper gastrointestinal tract, may be diminished by the enteric coating of mycophenolate sodium.

Mycophenolate mofetil displays a similar gastrointestinal adverse event profile to NSAIDs, and both are lipid soluble.[104] The incidence of dyspepsia was 40% with mycophenolate mofetil and 45% with NSAIDs in short-term studies. Incidences of ulcer perforation and gastrointestinal bleeding were 3–8% for mycophenolate mofetil within 6 months, compared with 0.5–4% for NSAIDs within 1 year.[104] The physicochemical properties of NSAIDs are implicated in short-term NSAID-induced gastrointestinal toxicity. They lead to interactions with surface phospholipids and uncoupling of mitochondrial oxidative phosphorylation. Topical damage results at the surface of the gastrointestinal tract.[104] Based on the common physicochemical properties and observed toxicities between NSAIDs and MPA, it is hypothesised that MPA may also uncouple oxidative phosphorylation. Preliminary results confirmed the potency of MPA to uncouple mitochondrial oxidative phosphorylation.[104] Enteric coating of NSAIDs reduced the incidence of ulceration by 25–70%.[104] Both ERL studies did not reveal a dramatic reduction of upper or non-upper gastrointestinal adverse events in the EC mycophenolate sodium groups.[61,62] There was a trend towards a lower mean gastrointestinal adverse event severity score at 3, 6 and 12 months in the ERL B302 study, without reaching statistical significance.[61] The similar symptoms and frequencies of EC mycophenolate sodium- and mycophenolate mofetil-related gastrointestinal adverse events suggest that their rise originates from the antiproliferative effect of MPA on intestinal IMPDH.[104]

6. Conclusion

Individual noncompliance in transplant recipients is underestimated, often unpredictable, and to date not sufficiently analysed. EC mycophenolate sodium appears to be similar to mycophenolate mofetil with regard to safety and efficacy in kidney transplant recipients, and both drugs share the same profile of adverse drug events that might increase medication nonadherence. Enteric coating did not significantly reduce the rate of gastrointestinal symptoms. Monitoring of MPA plasma concentrations may be useful to control compliance with EC mycophenolate sodium and mycophenolate mofetil and to adjust dosage.

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