Drugs 2005; 65 (6): 799-805
0012-6667/05/0006-0799/$39.95/0

Mycophenolate Sodium Delayed Release

Prevention of Renal Transplant Rejection

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Contents

Abstract

▲ Mycophenolate sodium delayed release is an enteric-coated formulation designed to release the active agent (mycophenolic acid) in the small intestine.

▲ Mycophenolate sodium delayed release was equivalent in efficacy to, and had a similar tolerability profile as, mycophenolate mofetil in *de novo* renal transplant patients treated with ciclosporin (cyclosporin) and corticosteroids in a well designed study of 12 month's duration.

▲ Maintenance renal transplant patients treated with ciclosporin and corticosteroids were converted from mycophenolate mofetil to mycophenolate sodium delayed release without any alteration in efficacy or tolerability in a well designed study of 12 month's duration.

▲ The incidence of gastrointestinal adverse events with mycophenolate sodium delayed release was similar to that with mycophenolate mofetil.

Features and properties of mycophenolate sodium delayed release (Myfortic®) in renal transplant patients	
Indication	
Prophylaxis of organ rejection in patients receiving allogeneic renal transplants treated with ciclosporin (cyclosporin) and corticosteroids	
Mechanism of action	
Inhibition of inosine monophosphate dehydrogenase	
Dosage and administration	
Recommended dosage	720mg
Route of administration	Oral
Frequency of administration	Twice daily
Mean steady-state pharmacokinetics of mycophenolate sodium delayed release 720mg twice daily in stable renal transplant recipients	
Peak plasma concentration (C_{max})	19.2 μg/mL
Area under the plasma concentration-time curve	56.0 μg • h/mL
Time to C_{max}	≈2 hours
Elimination half-life	8–16 hours
Adverse events	
Most frequent	Gastrointestinal adverse events

Inhibitors of inosine monophosphate dehydrogenase (IMPDH) are effective immunosuppressants. However, mycophenolate mofetil, a commonly used IMPDH inhibitor, is associated with a high incidence of gastrointestinal (GI) adverse events.[1] This leads to dose reductions or treatment withdrawals and, consequently, efficacy is often compromised. In an attempt to avoid upper GI tract irritation, an enteric-coated formulation of mycophenolate sodium has been developed that delays the release of the active agent mycophenolic acid (MPA) until the small intestine.[2]

This profile focuses on data relevant to the use of oral mycophenolate sodium delayed release (Myfortic®)[1] in the prevention of rejection of allogeneic renal transplants.

1. Pharmacodynamic Profile

- MPA is a selective, uncompetitive and reversible inhibitor of IMPDH, the rate-limiting enzyme in the *de novo* pathway of guanosine nucleotide synthesis.[1] Guanosine triphosphate is needed for lymphocytes to undergo mitogenic transformation. Thus, MPA has a selective antiproliferative effect on lymphocytes which rely on the *de novo* synthesis of purines. Since other cell types are able to utilise salvage pathways of purine synthesis, MPA has a more potent cytostatic effect on lymphocytes than other cells.[1]
- The depletion of guanosine nucleotide stores by MPA also interferes with the glycosylation of adhesion molecules, thus potentially interfering with the ability of the lymphocytes to attach and invade an allograft endothelium.[1] MPA also alters the expression of cell surface T-cell activation markers and cytokines and induces lymphocyte apoptosis.[3]
- In 14 stable renal transplant patients, predose IMPDH activity in peripheral mononuclear cells was lower with mycophenolate sodium delayed release 720mg twice daily than with mycophenolate mofetil 1000mg twice daily (5.4 vs 9.8 nmol/h/mg; $p < 0.01$) [equimolar dosage of MPA].[4] However, the daytime mean IMPDH activity (measure of overall pharmacodynamic response) was similar in the two groups (4.9 vs 5.8 nmol/h/mg).
- Mycophenolate sodium delayed release prevented acute rejection of renal transplants in animal models.[5,6] In a rat model of renal transplantation, mycophenolate sodium delayed release in combination with ciclosporin (cyclosporin) enabled long-term survival of the animals without histological signs of rejection.[5]
- Mycophenolate sodium delayed release prevented intimal thickening in a rat aorta transplantation model, suggesting that this agent has a positive effect on chronic graft vasculopathy.[5]
- Mycophenolate sodium delayed release decreased antibody production in mice.[2]

2. Pharmacokinetic Profile

- *In vitro*, MPA is not released from the delayed-release formulation of mycophenolate sodium under acidic conditions (such as in the stomach), but is highly soluble in neutral conditions (such as in the intestine).[2]
- MPA is almost completely absorbed (93%), and had an absolute bioavailability of 72% when mycophenolate sodium delayed release was administered in combination with ciclosporin microemulsion in stable renal transplant patients.[2]
- The pharmacokinetics of a single oral dose of mycophenolate sodium delayed release were dose proportional and linear over 180–2160mg in stable renal transplant patients.[7]
- Mean systemic MPA exposure (area under the plasma concentration-time curve; AUC) was similar with mycophenolate sodium delayed release 720mg and mycophenolate mofetil 1000mg after a single

1 The use of trade names is for product identification purposes only and does not imply endorsement.

dose (62.1 vs 60.8 μg • h/mL)[8] and with twice-daily administration at steady state (56.0 vs 55.7 μg • h/mL)[4] in stable renal transplant patients (n = 24[8] and 14;[4] data presented in abstracts). Respective mean maximal plasma MPA concentrations (C_{max}) were also similar after a single dose (26.1 vs 30.2 μg/mL)[8] and with twice-daily administration at steady state (19.2 and 20.2 μg/mL).[4]

- Consistent with the release of MPA from the enteric-coated formulation in the intestine rather than the stomach, the median time to MPA C_{max} (t_{max}) was longer with mycophenolate sodium delayed release than with mycophenolate mofetil after a single dose (2.0 vs 0.8 hours)[8] or with twice-daily administration at steady state (2.3 vs 0.9 hours; $p < 0.01$)[4] in stable renal transplant recipients.

- At equivalent dosages of mycophenolate sodium delayed release (based on body surface area), the mean C_{max} and AUC of MPA were higher by 33% and 18% in paediatric renal transplant patients than in adults.[2] In 16 stable paediatric renal transplant patients (aged 5–16 years) administered a single dose of mycophenolate sodium delayed release 450 mg/m^2, C_{max}, AUC and t_{max} of MAP were 31.9 μg/mL, 74.5 μg • h/mL and 2.5 hours, respectively (data presented as an abstract).[9]

- The pharmacokinetics of mycophenolate sodium delayed release 720mg twice daily during the early transplant period were different to those determined later after transplantation.[7] Mean MPA AUC increased from day 14 to 180 by 91% (from 29.1 to 55.7 μg • h/mL) and the mean MPA C_{max} increased by 65% (from 13.9 to 23.0 μg/mL) in 27 *de novo* renal transplant patients treated with mycophenolate sodium delayed release in a subset analysis of a randomised, double-blind study.[7]

- Coadministration of mycophenolate sodium delayed release 720mg with a high fat meal had no effect on systemic exposure to MPA, but reduced C_{max} by 33% and delayed t_{max} by 5 hours.[2]

- MPA is highly protein bound (>98%). Its mean volume of distribution at steady state is 54L and at elimination phase is 112L.[2]

- MPA is primarily metabolised in the liver by glucuronyl transferase to an inactive metabolite, mycophenolic acid glucuronide (MPAG), the major urinary excretion product.[1] Urinary excretion of MPA is negligible (≈3%).[2] MPAG is also excreted in the bile, but glucuronidases from gut bacteria convert it back to MPA, which is reabsorbed and recirculated.

- The mean elimination half-life of MPA is 8–16 hours, with a mean renal clearance of 140 mL/min in stable renal transplant patients.[2] Respective values for MPAG were 13–17 hours and 15.5 mL/min.

Drug Interactions

- At steady state, mycophenolate sodium delayed release did not affect the pharmacokinetics of ciclosporin.[2]

- In stable renal transplant recipients treated with mycophenolate sodium delayed release, MPA plasma exposure was increased (by 19%) in patients receiving concurrent tacrolimus versus concurrent ciclosporin microemulsion.[10]

- Coadministration of mycophenolate sodium delayed release and antacids decreased the mean MPA AUC and C_{max} by 37% and 25%.[2]

- Levels of aciclovir and ganciclovir (and MPAG) are increased if these agents are coadministered with mycophenolate sodium delayed release in patients with renal impairment.[2]

- Concurrent administration of mycophenolate sodium delayed release and a bile acid sequestrant (e.g. cholestyramine) interrupted enterohepatic recirculation and reduced MPA exposure.[2]

- Mean levonorgestrel AUC was decreased by 15% during concomitant administration of mycophenolate mofetil and the oral contraceptive.[2] Caution is therefore advised when mycophenolate

sodium delayed release is administered with oral contraceptives.[2]

3. Therapeutic Efficacy

The efficacy of mycophenolate sodium delayed release 720mg twice daily has been compared with that of mycophenolate mofetil 1000mg twice daily in *de novo* (n = 423)[11] or maintenance (n = 322)[12] renal transplant recipients (aged 18–75 years) receiving ciclosporin microemulsion, with[11,12] or without[12] corticosteroids, in two randomised, double-blind, multicentre studies.

In the *de novo* study,[11] the primary endpoint was the incidence of treatment failure (biopsy-proven acute rejection, graft loss, death or loss to follow-up within 6 months of treatment). Mycophenolate sodium delayed release was considered to be clinically equivalent to mycophenolate mofetil when the 95% CI was within the predetermined interval (−12, +12).

In the 12-month maintenance study, patients were at least 6 months post-transplant and had received mycophenolate mofetil 1000mg twice daily in combination with ciclosporin microemulsion, with or without corticosteroids, for at least 4 weeks prior to screening.[12] Efficacy was assessed as a secondary endpoint, by measuring the incidence of treatment failure (biopsy-proven acute rejection, graft loss or death). The incidence of biopsy-proven chronic rejection was also assessed.

De Novo Renal Transplant Patients

- Mycophenolate sodium delayed release had equivalent therapeutic efficacy to mycophenolate mofetil in *de novo* renal transplant recipients.[11] An equivalent proportion of patients experienced treatment failure at 6 months (25.8% vs 26.2%; 95% CI −8.7, +8.0).
- Rates of treatment failure, biopsy-proven acute rejection and biopsy-proven chronic rejection were not significantly different between the two treatment groups at 12 months (figure 1). In patients with biopsy-proven acute rejection, the incidence of severe acute rejection was 2.1% with mycophenolate sodium delayed release and 9.8% with mycophenolate mofetil.

Maintenance Renal Transplant Patients

- Mycophenolate sodium delayed release was as effective as mycophenolate mofetil in maintenance renal transplant patients who had previously been treated with mycophenolate mofetil.[12] At 12 months, there were no significant differences in rates of treatment failure, biopsy-proven acute rejection or biopsy-proven chronic rejection between those who were treated with mycophenolate sodium delayed release and those who remained on mycophenolate mofetil (figure 2).

4. Tolerability

- The tolerability profile of mycophenolate sodium delayed release was similar to that of mycopheno-

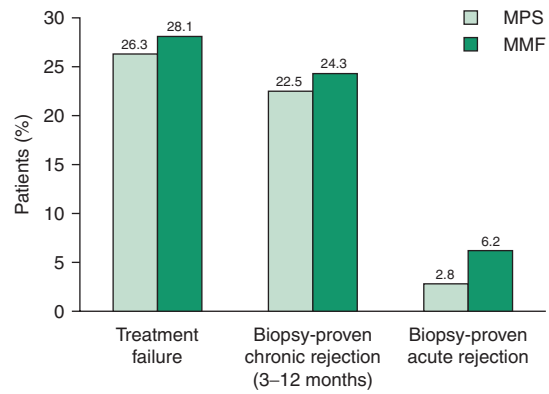

Fig. 1. Efficacy of mycophenolate sodium delayed release (MPS) in *de novo* renal transplant recipients at 12 months.[11] In a randomised, double-blind, multicentre study, patients were treated with MPS 720mg twice daily (n = 213) or mycophenolate mofetil (MMF) 1000mg twice daily (n = 210). Patients received otherwise identical immunosuppressive regimens (ciclosporin [cyclosporin] microemulsion and corticosteroids) and cadaveric (84%) or living-unrelated or living-related non-HLA-identical donor kidney transplants. Treatment failure was defined as the first occurence of biopsy-proven acute rejection, graft loss, death or loss to follow-up. There was no significant between-group difference for any parameter.

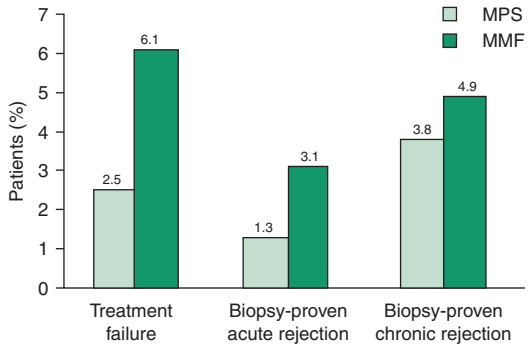

Fig. 2. Efficacy of mycophenolate sodium delayed release (MPS) in maintenance renal transplant patients at 12 months.[12] In a randomised, double-blind, multicentre study, renal transplant patients were at least 6 months post-transplant and had received mycophenolate mofetil (MMF) 1000mg twice daily in combination with ciclosporin (cyclosporin) microemulsion, with or without corticosteroids, for at least 4 weeks prior to screening. After a 2-week run-in period, patients were randomised to MPS 720mg twice daily (n = 159) or MMF 1000mg twice daily (n = 163). Efficacy was evaluated as a secondary endpoint. Treatment failure was defined as the incidence of biopsy-proven acute rejection, graft loss or death.

late mofetil during a 12-month period in *de novo*[11] and maintenance[12] renal transplant patients, with no significant between-group difference in the incidence of overall or suspected drug-related adverse events (figure 3) [see section 3 for study details].

- Maintenance renal transplant patients can be converted from mycophenolate mofetil to mycophenolate sodium delayed release without any change in the tolerability profile.[12] The incidence of GI adverse events at 3 months (primary endpoint) in the patients who switched to mycophenolate sodium delayed release was not significantly different to that in patients who remained on mycophenolate mofetil (26.4% vs 20.9%; 95% CI not reported). The incidence of neutropenia (<1500 cells/mm^3) at 3 months (primary endpoint) in mycophenolate sodium delayed release recipients was not significantly different to that in mycophenolate mofetil recipients (0.6% vs 3.1%; 95% CI −6.74, +0.80] and remained unchanged for the rest of the 12-month study.[12] Clinical equivalence was established when the upper limit of the 97.5% CI of the difference in the incidence of the adverse event was <10%.

- GI adverse events were the most commonly reported adverse events, with a similar incidence in both treatment groups in each 12-month analysis (figure 3).[11,12] In *de novo* renal transplant patients treated with mycophenolate sodium delayed release or mycophenolate mofetil, constipation (38% vs 40%), nausea (29% vs 27%), diarrhoea (24% vs 25%), vomiting (23% vs 20%) and dyspepsia (23% vs 19%) were commonly reported.[2] In maintenance renal transplant recipients, nausea (25% vs 19%) and vomiting (21% vs 25%) were commonly reported.[2]

- In *de novo* renal transplant patients, dose changes (interruptions, adjustments or discontinuations) due to GI adverse events during the 12 months were similar in mycophenolate sodium delayed release and mycophenolate mofetil recipients (15.0% vs 19.5%). In maintenance renal transplant patients, dose reductions and/or treatment interruptions (4.4% vs 5.5%) and dose discontinuations (1.9% vs 1.8%) were similar in the two treatment groups.

- The overall incidence of infections was similar between the two treatment groups in *de novo*[11] and maintenance[12] renal transplant recipients during a 12-month period, as was the incidence of cytomegalovirus infection (figure 3). Urinary tract infection was commonly reported in *de novo* renal transplant patients (29.1% vs 33.3%).[11]

- In mycophenolate sodium delayed release recipients compared with mycophenolate mofetil recipients, there was a lower incidence of serious infections in maintenance renal transplant patients (8.8% vs 16.0%; $p < 0.05$)[12] and a lower incidence of serious pneumonia in *de novo* transplant patients (0.5% vs 4.3%; $p = 0.01$).[11]

- In stable paediatric (mean age 14 years) renal transplant patients (n = 19) converted from mycophenolate mofetil 457 mg/m^2 twice daily to mycophenolate sodium 432 mg/m^2 twice daily, the

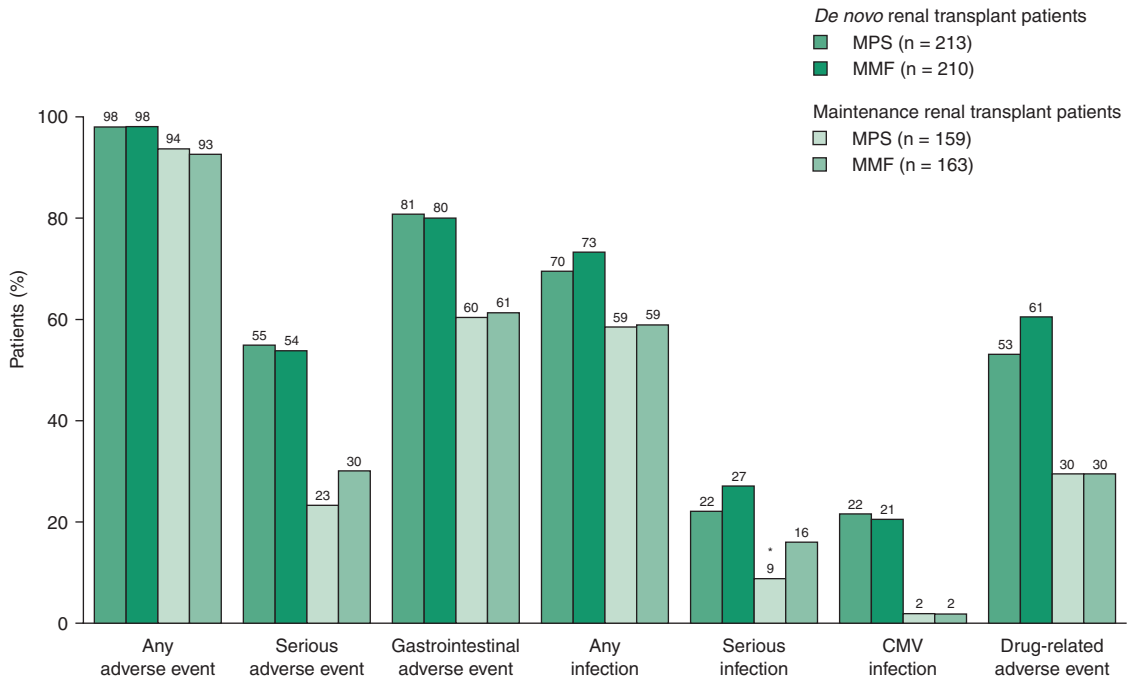

Fig. 3. Comparative tolerability of mycophenolate sodium delayed release (MPS) and mycophenolate mofetil (MMF) in *de novo*[11] or maintenance[12] renal transplant patients during a 12-month period. Patients were enrolled in randomised, double-blind, multicentre studies and were treated with MPS 720mg twice daily or MMF 1000mg twice daily in combination with ciclosporin (cyclosporin) microemulsion and corticosteroids. *De novo* transplant patients had cadaveric (84%) or living-unrelated or living-related non-HLA-identical donor kidney allografts.[11] Maintenance renal transplant patients were at least 6 months post-transplant and had previously been treated with MMF.[12] **CMV** = cytomegalovirus; * $p < 0.05$ vs MMF.

incidence of adverse events was 63% (42% were GI, 16% upper GI and 21% diarrhoea).[13] In this 6-month open-label trial, patients also received ciclosporin microemulsion and corticosteroids. The incidence of infections was 53% and there was no change in laboratory parameters throughout the trial.

5. Dosage and Administration

Mycophenolate sodium delayed release 720mg twice daily (administered in combination with ciclosporin and corticosteroids) is indicated for the prophylaxis of organ rejection in adult patients receiving allogeneic renal transplants.[2,14]

In the US, the recommended dosage of this agent in stable paediatric patients is 400 mg/m^2 body surface area administered twice daily (up to a maximum of 720mg twice daily).[2] According to UK prescribing information, insufficient data are available to support the efficacy and safety of mycophenolate sodium delayed release in children.[14]

No dosage adjustments are considered necessary in patients experiencing delayed graft function postoperatively, the elderly or patients with hepatic parenchyma disease. Patients with severe chronic renal impairment should be carefully monitored.[2]

6. Mycophenolate Sodium Delayed Release: Current Status

Mycophenolate sodium delayed release is currently approved in a number of regions including the US, Europe, Latin America, Asia and Australasia for the use in the prevention of renal transplant rejection.[15,16]

Mycophenolate sodium delayed release was equivalent in efficacy to, and had a similar tolerability profile as, mycophenolate mofetil in *de novo* renal transplant patients concurrently treated with ciclosporin and corticosteroids. Moreover, maintenance renal transplant patients treated with ciclosporin, with or without corticosteroids, were converted from mycophenolate mofetil to mycophenolate sodium delayed release without any alteration in efficacy or tolerability.

The large (n ≈ 1800), prospective, open-label, multicentre myPROMS (myfortic Prospective Multicentre Study) is currently being conducted to assess the efficacy and tolerability of mycophenolate sodium delayed release in combination with ciclosporin microemulsion in *de novo* and maintenance renal transplant patients. In particular, the effect of different patient demographics, various corticosteroid regimens and ciclosporin microemulsion targets will be investigated.[17] In addition, the open-label, multicentre PROGIS (Patient Reported Outcome on GastroIntestinal Symptoms) study will assess the effect on gastrointestinal symptom severity and health-related quality of life of converting maintenance renal transplant patients from treatment with mycophenolate mofetil to mycophenolate sodium delayed release.[18] The study plans to enrol 300 patients and will be 4–6 weeks in duration.

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