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Safety Assessment of the Conversion From Mycophenolate Mofetil to Enteric-Coated Mycophenolate Sodium in Stable Renal Transplant Recipients

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ABSTRACT

The immunosuppressant mycophenolate mofetil (MMF; CellCept) has greatly improved transplant recipients' clinical outcomes, but its efficacy may be limited by dose adjustments due to adverse events (AEs). An enteric-coated formulation of mycophenolate sodium (EC-MPS; *myfortic*), designed to improve gastrointestinal tolerability is now available.

This Latin-American, prospective, multicenter, open-label, 6-month trial assessed the safety and tolerability of converting renal transplant recipients from MMF to EC-MPS. In total, 237 renal transplant recipients (stable ≥ 3 months' posttransplant) receiving MMF (≤1000 mg b.i.d.) were enrolled. Adults (n = 218) were converted to EC-MPS 720 mg b.i.d. (equimolar to MMF 1000 mg b.i.d.) even if they were initially receiving <1000 mg MMF b.i.d. (ie, 47 adults received a higher than equimolar dose of EC-MPS). Children (n = 19) were converted to EC-MPS 450 or 432 mg/m^2 b.i.d. Patients also received cyclosporine microemulsion (Neoral) and corticosteroids.

There were three acute rejections and no graft failures. The incidence of AEs was 59.9% (in those receiving a higher than equimolar EC-MPS dose it was 57.4%). In all, 22% of patients had gastrointestinal AEs, 37% had infections, and 4.8% had hematological AEs. Only 24 patients (10%) had an AE-related dose reduction. Seven of these patients had received higher than equimolar doses of EC-MPS. Patients can be safely converted from different doses of MMF to a standard dose of EC-MPS. The requirement for EC-MPS dose reduction to manage AEs was relatively low. Use of EC-MPS is a valid alternative for renal transplant recipients receiving maintenance MMF treatment.

WHILE the efficacy of mycophenolate mofetil (MMF; CellCept) as an immunosuppressive agent for preventing graft rejection in kidney transplant recipients is well documented,[1,2] some concerns remain over its tolerability profile. The occurrence of adverse events, such as gastrointestinal (GI) disturbances and hematological abnormalities, may need dosing changes in the form of dose reduction, temporary interruption, or even withdrawal of therapy[3]—possibly compromising treatment. Several investigators have noted frequent dose changes in studies of MMF, and they have found that such changes are associated with adverse outcomes for the patient.[4,5] MMF is a prodrug that is metabolized to the active compound mycophenolic acid (MPA) in vivo. A different formulation for delivering MPA, enteric-coated mycophenolate sodium (EC-MPS; *myfortic*) has recently been developed.[6] The enteric coating delays drug release. Data from key studies have demonstrated the efficacy and tolerability of EC-MPS for maintaining graft survival in de novo and maintenance renal transplant patients.[7,8] Salvadori et al[7] have also shown the therapeutic equivalence of EC-MPS to MMF. When prescribed in equimolar doses, EC-MPS and MMF are bioequivalent in terms of key

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pharmacokinetic and pharmacodynamic parameters, such as exposure to MPA.[9]

The *myfortic* Prospective Multicenter Study (*my*PROMS) is an international clinical trial designed to assess the efficacy and safety of EC-MPS (combined with cyclosporine [CyA] microemulsion [Neoral]) in a large population of either de novo or maintenance renal transplant recipients.[10] The *my*PROMS features 14 subprotocols that address specific aspects EC-MPS therapy. The present study refers to a Latin American *my*PROMS substudy (LA01), the specific objective of which was to evaluate the safety of converting maintenance renal transplant patients from MMF to EC-MPS therapy. Following the publication of a 3-month interim analysis,[11] we present data from the final 6-month analysis.

METHODS

In accordance with the *my*PROMS protocol, LA01 was a prospective, 6-month, open-label study, and was conducted in multiple centers in seven Latin American countries (Argentina, Brazil, Colombia, Guatemala, Mexico, Peru, and Venezuela).

Following a screening phase, children and adults were eligible for inclusion in the study if they were receiving MMF as maintenance therapy following primary or secondary renal transplantation. They had to be stable for at least 3 months following transplantation with a baseline creatinine level <2.3 mg/dL. All patients were converted from MMF to EC-MPS upon entering the study, initially receiving 720 mg b.i.d. (equimolar to MMF 1000 mg b.i.d.). Those patients receiving <1000 mg b.i.d. MMF at study entry were highlighted, but were still prescribed EC-MPS 720 mg b.i.d. (a higher than equimolar dose) if deemed appropriate by the investigator. Patients continued to receive Neoral and corticosteroids. Neoral doses were adjusted according to blood concentrations 2 hours after dosing (C_2 monitoring), while corticosteroids were given according to the standards of individual centers. Postbaseline, patients were followed up at 2 weeks, 4 weeks, 3 months, and 6 months.

RESULTS

Population Characteristics

Between April 2002 and April 2003, a total of 237 patients were recruited into the LA01 substudy. The baseline characteristics of this population are described in Table 1. At study entry, 64 patients (27%) were receiving a lower than usual dose of MMF (ie, <2 g/d). This was the result of either standard site practice or because the patient had a history of adverse events (mainly GI). The adult patients in this subgroup (n = 47) did not differ significantly from the main population in their baseline characteristics. Their mean age was 39.1 ± 13.6 years, 59% were male and the mean time since transplant was 2.6 ± 2.4 years. Neoral therapy remained constant throughout the study, with a mean dose of 205.86 ± 127.15 mg/d at baseline and 202.82 ± 145.20 mg/d at 6 months. Mean C_2 values were 746.63 ng/mL at baseline and 727.17 ng/mL at month 6.

Conversion of Patients From MMF to EC-MPS

On entering the study, 171 adult patients were converted from MMF 1000 mg b.i.d. to EC-MPS 720 mg b.i.d. The 47 adults who were receiving a lower dose of MMF (700 ± 75 mg b.i.d.) were also converted to EC-MPS 720 mg b.i.d. (ie, they were converted to a higher than equimolar dose of MPA). Seventeen children originally receiving a mean MMF dose of 440 ± 147 mg/m^2 b.i.d. were prescribed EC-MPS 432 ± 51 mg/m^2 b.i.d. when they entered the trial; similarly, two children who were recruited receiving MMF 600 mg/m^2 b.i.d. were subsequently assigned EC-MPS at 450 mg/m^2 b.i.d.

Table 1. Patient Baseline Characteristics

Characteristic	
Total population (n)	237
Adults	218
Children (6–18 years)	19
Receiving MMF dose <2 g/d at baseline	64
Adults	47
Children	17
Male gender (n [%])	139 (59)
Race (n)	
Caucasian	112
African America	13
Other (Mestizos, Mulattoes, Indians)	112
Mean age	39.1 ± 13.8 years
Mean time since transplantation	2.6 ± 2.4 years
Creatinine	1.30 ± 0.34 mg/dL

Efficacy

No patients experienced graft failure during the study, but there were three cases of acute rejection in adult patients (two acute rejection episodes were classified as Banff category I and the other as Banff category II). In each case, rejection responded to treatment with corticosteroids.

Adverse Events

Adverse events are summarized in Table 2 for the whole study population and for the group of adults who were assigned a higher than equimolar dose of EC-MPS at conversion. In all, 142 patients (59.9%) were reported as having at least one adverse event, with infections predominating. More specifically, there were 88 episodes of infection. Of 27 viral infections, 10 cases were herpes-related, 8 were influenza, 2 were CMV, 1 was GI, and 1 was an upper respiratory infection (5 cases were unclassified). Further-

Table 2. Adverse Events

Adverse Event (AE)	Total Population (n = 237) (%)	Adults Receiving > Equimolar EC-MPS (n = 47) (%)
Patients with ≥1 AE	59.9	57.4
Gastrointestinal AE	22.0	29.7
Upper-gastrointestinal AE	12.6	17.0
Diarrhea	10.9	10.6
Hematological AE	4.8	6.4
Infections	37.0	29.8

more, investigators identified 24 fungal infections in their patients (14 pitiriasis versicolor, 8 onychomicosis, and 2 oral candiasis) and thirty seven bacterial infections (23 urinary tract, 3 gastroenteritis, 2 tonsilitis, 3 pneumonia, 2 subcutaneous abcesses, and 4 unclassified). All infections were judged to be mild or moderate in severity except for one episode of severe pneumonia. There were 38 episodes of upper GI disturbance including nausea (10 episodes), dyspepsia (6), epigastralgia (9), gastritis (3), stomach ache (4), and vomiting (6). Twelve hematological adverse events also occurred, including 5 leukopenias, 5 anemias, and 2 cases of erythrocytosis.

Other severe adverse events included a death (car accident), a suicide attempt, chest pain, heart failure decompensation, cholecystolithiasis, diarrhea, and fever of unknown etiology. Two patients developed skin neoplasias (one squamous cell and one epidermal). There were no cases of lymphoma. Laboratory safety variables remained stable throughout the 6-month trial in both the whole study population and in those patients receiving a higher than equimolar dose of EC-MPS (Table 3).

Dose Adjustment

Within the total study population, 24 patients (10%) required a reduction in their EC-MPS dose to manage an adverse event. Dose reductions associated with diarrhea (10 patients), hyperbilirubinemia (4), leukopenia (4), abdominal pain (2), cholecystolithiasis (2), anemia (1), and hyperuricemia (1). Seven patients who were converted to a higher than equimolar dose of EC-MPS subsequently had their dose reduced, 2 as a result of diarrhea, 2 because of leukopenia, and 3 because of abdominal pain, hyperbilirubinemia, and cholecystolithiasis.

Overall, 2% of patients required dose adjustments as a result of hematological adverse events, while 5% had EC-MPS dose adjusted because of a GI adverse event. All adverse events except cholecystolithiasis subsided following dose reduction.

DISCUSSION

The present study demonstrates that patients receiving MMF can be easily and safely converted to therapy with EC-MPS at a dose that provides an equimolar amount of MPA (EC-MPS 720 mg b.i.d.). This latest 6-month analysis confirms the findings of a 3-month interim analysis of 93 patients,[11] although the overall rate of patients experiencing one or more adverse events did increase as the study progressed (40.9% vs 59.9% at 3 and 6 months, respectively). The continued efficacy of MPA when delivered as EC-MPS was evident from the lack of graft failure and low incidence of rejection episodes in the 6 months following conversion. Data from our study therefore support the findings of other researchers who have safely converted maintenance renal transplant patients from MMF to EC-MPS with follow-up extending as far as 1 year.[8]

Our data also suggest that the many adult patients receiving a less than optimal dose of MMF (possibly because of poor tolerability) can be converted to a full therapeutic dose of EC-MPS without significantly reducing tolerability. Indeed, the rate of adverse events was similar for the whole population and this subgroup of patients; the incidence of diarrhea and infections did not differ, but upper GI side effects were slightly more frequent.

Overall, the incidence of GI side effects was relatively low at 22%. In contrast, randomized studies of MMF 2 g/d in renal transplant patients have elucidated rates of GI adverse events up to 45%.[3] Following conversion to EC-MPS, relatively few patients required dose adjustments. Only 24 patients (10%) had their dose reduced during 6 months of observation. Salvadori et al[7] have previously shown a trend toward less frequent dose change among de novo renal transplant recipients receiving EC-MPS compared with those receiving MMF. In our study, 7 of the patients with dose changes were among the 47 adult patients who were converted to a higher than equimolar dose of EC-MPS. This indicates that 85% of these patients were able to tolerate the full dose of EC-MPS. It is therapeutically desirable to maintain patients at stable doses of MPA treatment. Studies of patients receiving MMF have not only highlighted the frequency of dose change, but also that such changes are associated with poor outcomes for patients.

For example, in their study, Pelletier et al[5] found that 70.3% of patients had their MMF dose changed during the first year postrenal transplant. These patients were at significantly higher risk of acute rejection and graft failure than were patients whose MMF dose remained stable. Similarly, Knoll et al[4] found that risk of rejection increased by 4% for every week that MMF is given below full dose.

Table 3. Laboratory Safety Values

Population	Sample Time	Hb (g/dL)	WBC (10^3 cells/mm^3)	Neutrophils (10^3 cells/mm^3)	Platelets (10^3 cells/mm^3)	Creatinine (mg/dL)
Total population (n = 237)	Base	13.58 ± 2.16	8.34 ± 2.34	6.38 ± 1.11	248 ± 73	1.30 ± 0.34
	Month 6	13.49 ± 2.16	8.40 ± 2.68	6.41 ± 1.14	255 ± 78	1.27 ± 0.34
Adults receiving > equimolar EC-MPS (n = 47)	Base	13.4 ± 2.3	7.9 ± 2.7	6.4 ± 0.9	242 ± 91	1.3 ± 0.3
	Month 6	13.5 ± 2.4	7.9 ± 3.1	6.5 ± 1.0	244 ± 85	1.3 ± 0.3

All values are mean ± SD. Hb, hemoglobin; WBC, white blood cell.

Dose reductions were made primarily as a result of leukopenia, but also because of GI symptoms in 22% of patients.

We conclude that it is safe to convert maintenance renal transplant patients from MMF to EC-MPS. Additionally, patients receiving suboptimal doses of MMF may be able to tolerate full therapeutic doses of EC-MPS. Therefore, EC-MPS is a valid alternative to MMF in maintenance renal transplant patients, possibly helping to minimize risk of GI adverse events and dose change.

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