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A multicenter experience with generic mycophenolate mofetil conversion in stable liver transplant recipients

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Purpose: Generic substitution of brand-name medications can lead to significant cost savings and is an accepted medical practice. This study evaluated clinical and safety outcomes among liver transplant recipients whose mycophenolate mofetil (MMF) was converted from the brand-name formulation (Cellcept) to a generic formulation (My-rept).
Methods: Clinical data from multiple centers were prospectively collected for determination of complications, safety, and quality of life after in 154 clinically stable, adult liver transplant recipients whose MMF was converted to a generic formulation between April 2010 and September 2012. This protocol was approved by Institutional Review Boards of all involved sites.
Results: In eight patients (5.19%), nine instances of drug-related complications occurred after medication conversion. Half of these complications were gastrointestinal disorders (n = 4), and most (7 of 9) were mild. No significant differences were noted in mean pre- and postconversion gastrointestinal symptoms via a rating system (8.9 *vs.* 10.4) or gastrointestinal quality-of-life index scores (125.6 *vs.* 123.1). More than 90% of patients reported a status of "about the same" when questioned about the brand-name and generic formulation using the Patient Overall Treatment Effect and Investigator Overall Treatment Effect measures. The incidence of serious adverse events was 5.8%. Acute rejection occurred in two patients, with no graft loss or death.
Conclusion: Clinical experience as well as research data showed that generic MMF was comparable in efficacy to the brand-name drug. Given the lack of adverse events and the safety findings, conversion from brand-name MMF to generic MMF should be encouraged.
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Key Words: Drug-related side effects and adverse reactions, Generic drugs, Transplantation liver, Mycophenolate mofetil, Quality of life

INTRODUCTION

Mycophenolate mofetil (MMF) (Cellcept, Roche Pharmaceuticals AG, Basel, Switzerland) is used routinely as a combination immunosuppressant with calcineurin inhibitors (CNIs) after liver transplantation. MMF significantly decreases the rate of biopsy-proven acute rejection (BPAR) as compared with either placebo or azathioprine at 6 months after transplantation [1,2]. However, a high proportion of MMF-treated recipients suffer from gastrointestinal (GI) complications, such as watery diarrhea or abdominal pain. GI symptoms contribute significantly to the deterioration of

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health-related quality of life (HRQoL) in transplant recipients [3]. High proportions of patients receiving MMF require dose reductions or discontinue MMF treatment because of adverse GI events [4]. MMF dose reduction or discontinuation has a significant impact on transplant outcomes and is associated with a significantly higher incidence of acute rejection within the first posttransplant year, resulting in decreased 3-year graft survival [5].

The importance of generic versions of immunosuppressive agents has been recently studied [6,7]. As generic drugs do not require expensive drug development programs, their price is often considerably lower than that of the innovator product. Generic substitution is generally accepted and promoted by healthcare providers, health insurance companies and government agencies [8]. Unbranded and branded generic drugs accounted for 65.6% and 8.6%, respectively, of all drugs dispensed in the United States in 2009, revealing that 74.2% of all drugs dispensed are generic products [6].

In 2009, the Korea Food and Drug Administration (KFDA) approved the first generic formulation of MMF (My-rept), manufactured by Chong Kun Dang Pharmaceutical Co. (Seoul, Korea). The KFDA accepts two products as bioequivalent if tests of the generic product against the reference product have a 90% confidence interval within 80%–125% for relative mean maximum blood concentration (Cmax) and area under the plasma concentration-versus-time curve (AUC [0–t] or AUC [0–∞]). A typical bioequivalence study employs a single-dose, two-way crossover design in 24–40 healthy subjects, depending on the pharmacokinetic variability of the test compound, and data in the intended patient population are not required. However, transplant patients are vastly different from healthy subjects because they are subject to multiple comorbidities and concomitant pharmacotherapy that can influence drug disposition.

The use of generic MMF in the setting of liver transplantation is still a subject of discussion because bioequivalence to MMF has not been demonstrated and interference with CNI absorption and triggering of acute rejection are possible because of the retarded intestinal absorption of MMF. Additionally, there has been no investigation of one-way conversion from brand-name MMF to generic MMF published in the literature, so the tolerability and safety of MMF and its effects on patient quality of life are unknown.

Data describing conversion to generic MMF formulation in adult liver transplant recipients are scarce. This six-month, multicenter, single-arm, open-label study in maintenance liver transplant recipients aimed to investigate the efficacy, safety and tolerability of converting stable maintenance liver transplant patients from brand-name MMF to generic MMF.

METHODS

Study design

This study was a prospective trial conducted at four transplant centers between January 2010 and December 2012. Institutional Review Board (IRB) approval was obtained at each center (Samsung Medical Center IRB no. 9405, Seoul National University Hospital IRB no. 2009-P-000381/1, Konkuk University Hospital IRB no. 0912006049, Chonbuk University Hospital IRB no. 2009-P-000979/1). Each center used its own criteria to determine which patients to convert and when patients had stable graft function. Once a patient converted from brand to generic MMF (My-rept), all centers followed a plan of treatment consistent with other liver transplant recipients. Written informed consent was obtained prior to participation.

Inclusion criteria

Patients of either gender, aged 19 to 70 years, who received a primary or secondary liver transplant from a deceased or living donor and who were at least six months posttransplant were eligible. Patients were required to have received CNI and MMF for at least two months as part of their immunosuppressive regimen. Additionally, patients were to be in stable condition in terms of graft function, which was defined as within twice the upper limit for serum total bilirubin, AST, ALT at screening and baseline, have had no changes in immunosuppressive regimen due to graft dysfunction, and have no known clinically significant laboratory changes for at least two months before enrollment. Women of childbearing potential were required to have a negative pregnancy test.

Exclusion criteria

Patients were excluded if they were multiorgan recipients or had a previous transplant with any organ other than a liver. Additional exclusion criteria included evidence of graft rejection or treatment for acute rejection within three months prior to screening, leukopenia (<2,500/mm^3) and/or serum creatinine >2.0 mg/dL prior to enrollment, use of any other investigational drug within two weeks before screening, malignancy (other than local basal or squamous cell carcinoma of the skin) within the last five years or after liver transplantation, clinically significant infection requiring continued therapy, presence of severe GI complications such as diarrhea or severe peptic ulcer disease at screening, more than two discontinuations of MMF prior to screening, detection of recurrent hepatitis B virus infection (defined as positive hepatitis B surface antigen), receipt of antiviral therapy for HCV reinfection, positive HIV status, or evidence of drug or alcohol abuse. Women of childbearing potential who were unwilling to use an effective form of contraception for the duration of the study and for six weeks following study drug discontinuation and women who

were pregnant or lactating were also excluded.

Monitoring

All participants received care in the outpatient transplant clinic where weight, height, total bilirubin, albumin, serum creatinine, ALP, AST, ALT, gamma glutamyltranspeptidase (γ-GT) and graft rejection status were routinely monitored. A 1:1 dose conversion was applied in switching from the reference to the generic drug. Evaluations were performed at baseline (day of conversion to generic drug), 2, 4, and 6 months after conversion. Data were collected as planned for analysis. This trial was monitored internally and externally during the study period.

Safety evaluations

Evaluation of safety criteria included monitoring and recording all infections and adverse events, defined as any newly occurring condition or disability or worsening of a condition observed at baseline. Routine blood analysis, blood chemistry, vital signs, and physical examinations were performed regularly.

Efficacy evaluations

Efficacy was measured by rate of treatment failure, such as BPAR, liver graft loss, or death within six months of conversion to study medication. Liver graft function was assessed via liver function tests such as total bilirubin, albumin, ALP, AST, ALT, and γ-GT. All data were collected by the investigators, monitored by independent external personnel, and transferred to a database.

Rejection

Acute rejection episodes were proven with core biopsies before or within 24 hours following commencement of antirejection therapy and assessed according to the Banff classification [9]. Methylprednisolone was administered intravenously at 500 mg/day for three days. Study medication was not interrupted during antirejection therapy.

Quality of life assessment

Three questionnaires were used to examine patient' conditions: (1) Gastrointestinal Symptom Rating Scale (GSRS), (2) Gastrointestinal Quality-of-Life Index (GIQLI), and (3) Patient Overall Treatment Effect (P-OTE) and Investigator Overall Treatment Effect (I-OTE).

The GSRS is a 15-item instrument designed to assess symptoms associated with common GI disorders [10]. The GSRS consists of five subscales (reflux, diarrhea, constipation, abdominal pain, and indigestion) producing a mean subscale score ranging from 0 (no discomfort) to 6 (very severe discomfort). The GIQLI is a 36-item questionnaire that assesses the impact of GI disease on daily life [11]. The GIQLI has five subscales (GI symptoms, emotional status, physical functions, social functions, and stress of medical treatment) within the total score of 36 items. Lower scores represent greater dysfunction [10]. The OTE assesses changes in symptoms or HRQoL since the previous visit [12]. Respondents indicate the degree of improvement or worsening on a seven-point scale. Patients completed the GSRS and GIQLI at visits 1 (baseline) and 4 (after 24 weeks on generic drug treatment). The OTE was administered only at visit 4. Patients completed OTE questionnaires for symptoms and for HRQoL and physicians completed an OTE questionnaire for symptoms.

Statistical analyses

The safety population included all patients who received at least one dose of study medication and underwent at least one safety assessment following trial medication. The study was exploratory in nature and a control group was not included in the protocol. Continuous variables are presented as mean ± standard deviations and compared using the paired t-test or analysis of variance. Data are summarized for demographic and baseline characteristics. Assessment of safety was based on the frequency of adverse events and the number of laboratory values outside of predetermined ranges. $P < 0.05$ was considered significant. Analysis was performed using IBM SPSS

Table 1. Baseline participant characteristics

Characteristic	No. (%)
Age (yr)	
20–39	3 (2.0)
40–59	117 (76.0)
60–70	34 (22.0)
Gender	
Male	116 (75.3)
Female	38 (24.7)
Time from transplantation to conversion (mo)	
6–11	17 (11.0)
12–23	18 (11.7)
24–47	46 (30.0)
48–71	41 (26.6)
≥72	32 (20.8)
Diagnosis	
HBV	60 (39.0)
HBV, HCC	55 (35.7)
Alcoholic	12 (7.8)
Alcoholic, HCC	3 (1.9)
Toxic	3 (1.9)
HCC	4 (2.6)
Others	17 (11.0)
Type of transplantation	
Deceased donor	51 (33.1)
Living donor	103 (66.9)

HCC, hepatocellular carcinoma.

ver. 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

Patients

Patients undergoing liver transplantation from living or deceased donors were enrolled at four transplantation centers in South Korea between January 2010 and December 2012. A total of 154 patients (mean age, 53.8 years; men:women, 116:38) were screened and enrolled. Among the 154 enrolled patients, six were immediately excluded, and 140 patients completed the trial with eight drop-outs for violation of inclusion or exclusion criteria (n = 4), violation of study program (n = 3), or use of prohibited drugs (n = 1). Patient demographic information is presented in Table 1. The mean time since liver transplantation was 47.7 months; 33.1% of participants received a liver from a deceased donor and 66.9% from a living donor; 89.6% (n = 138) were treated with tacrolimus as concomitant immunosuppressive therapy, and 10.4% (n = 16) with cyclosporine. One hundred forty patients fulfilled the criteria for inclusion in per-protocol (PP) analysis, with 14 showing at least one major deviation from the protocol (Fig. 1).

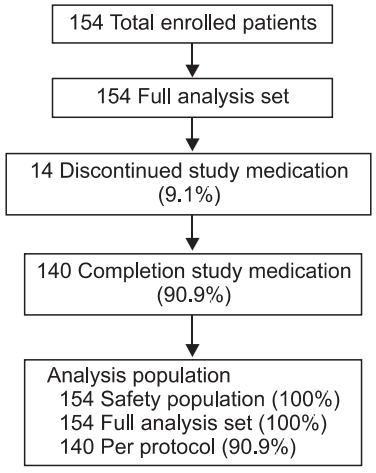

Fig. 1. Study population.

Adverse events

After conversion, the overall incidence of adverse events (AEs) was 48.1% (112 cases in 74 patients). Infections accounted for 27.7% (31/112) of all incidence, particularly upper respiratory tract infections (24 cases). GI events accounted for 21.4% (24 cases in 21 patients) including abdominal pain (5 cases), diarrhea (4 cases) and gastritis (3 cases). The incidence of hematologic AEs was 0.7% (one case of neutropenia). No patient discontinued the study medication due to an AE. Drug-related AEs occurred in nine cases in eight patients (Table 2), with nine cases of severe AEs in six patients (Table 3). All patients with serous AEs recovered. Only two patients (1.4%) experienced acute rejection during the study period and no episodes of death or graft loss occurred. No neoplasias or lymphomas were reported. During the six-month follow-up, no appreciable change was observed after conversion in biochemical indices of liver function such as total bilirubin, albumin, ALP, ALT, AST, or γ-GT (Table 4).

Gastrointestinal complications and quality of life

Mean GSRS score increased from 8.9 ± 9.3 at baseline (visit 1) to 10.4 ± 11.8 at visit 4. However, GIQLI score decreased from 125.6 ± 13.9 at baseline (visit 1) to 123.1 ± 16.0 at visit 4. No significant differences were observed in GSRS or GIQLI score between visit 1 (baseline) and visit 4 (last visit) (P = 0.060 for GSRS and P = 0.261 for GIQLI) (Fig. 2). P-OTE revealed that

Table 2. Adverse events

	No. of patients (%)	Cases
Adverse events	74 (48.1)	112
Drug-related adverse events	8 (5.2)	9
Serious adverse events	6 (3.9)	9
Drug-related serious adverse events	2 (1.4)	2

Table 3. Serious adverse events

Case	Adverse events	Degree	Treatments	Drug-related	Discontinuation of study drug
1	Acute rejection	Moderate	Increased IS	Unrelated	No
2	LFT elevation	Moderate	None	Related	No
3	Herpes zoster	Mild	Antiviral agent	Related	No
4	LFT elevation	Moderate	Steroids	Unrelated	No
5	IVC stenosis	Moderate	Liver biopsy	Unrelated	Yes
6	Ascites	Moderate	Liver biopsy	Unrelated	Yes
7	Hepatic congestion	Moderate	Liver biopsy	Unrelated	Yes
8	Spinal stenosis	Moderate	None	Unrelated	No
9	Obliterated hepatic vein	Moderate	None	Unrelated	Yes

LFT, liver function test; IVC, inferior vena cava.

Table 4. Laboratory results by visit

Variable	Visit 1	Visit 2	Visit 3	Visit 4	P-value
White blood cells (/μL)	5,343 ± 1,684	5,196 ± 1,578	5,321 ± 1,673	5,437 ± 1,865	0.316
Hemoglobin (g/dL)	14.6 ± 1.6	14.6 ± 1.6	14.6 ± 1.6	14.7 ± 1.7	0.410
Platelet (/μL)	161,650 ± 61,489	163,720 ± 65,533	160,590 ± 57,819	163,700 ± 55,447	0.190
Total bilirubin (mg/dL)	0.97 ± 0.51	0.96 ± 0.52	0.98 ± 0.52	1.00 ± 0.51	0.937
AST (IU/L)	23.7 ± 8.7	23.8 ± 9.4	25.4 ± 26.4	27.6 ± 29.4	0.791
ALT (IU/L)	21.8 ± 13.2	22.4 ± 15.0	23.2 ± 21.1	26.3 ± 30.9	0.822
ALP (IU/L)	85.5 ± 34.6	84.2 ± 33.4	85.1 ± 35.9	85.0 ± 32.0	0.441
γ-GT (IU/L)	49.6 ± 65.4	49.6 ± 62.9	49.5 ± 62.5	50.6 ± 49.5	0.211

Values are presented as mean ± standard deviation.
γ-GT, gamma glutamyltranspeptidase.

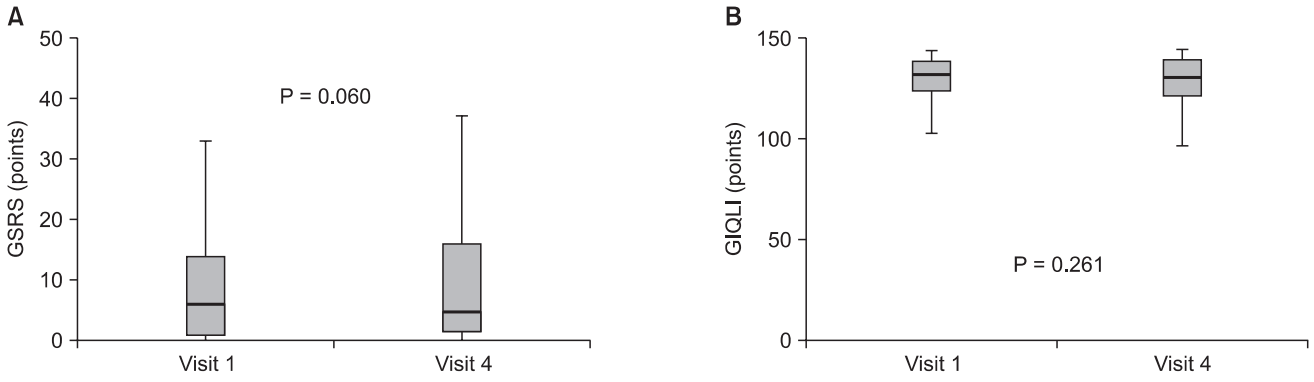

Fig. 2. Changes in GSRS (A) and GIQLI (B) scores between visit 1 (baseline) and visit 4. GSRS, Gastrointestinal Symptom Rating Scale; GIQLI, Gastrointestinal Quality-of-Life Index.

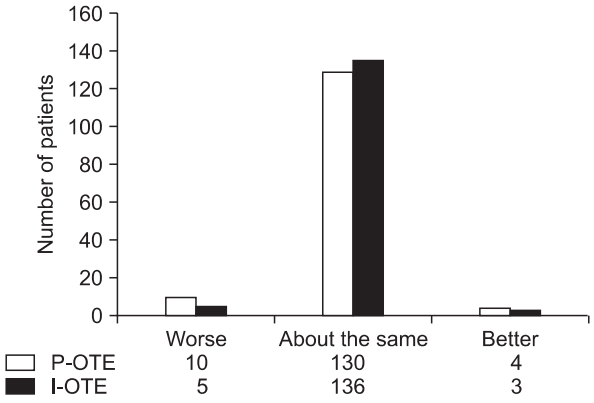

Fig. 3. Patient-reported and investigator-reported overall treatment effect on quality of life. P-OTE, patient overall treatment effect; I-OTE, investigator overall treatment effect.

90.3% of patients in the total PP population felt "about the same" with regard to participant-reported GI symptoms and quality of life after switching from brand-name to generic MMF. I-OTE showed that 94.4% of patients had the same GI symptoms and quality of life after conversion (Fig. 3).

DISCUSSION

The use of generic medications is widespread and represents a viable cost-saving opportunity in the face of rising health care costs [13]. However, while economics is a driving force behind utilization of generic drug products, patient welfare must remain the principal consideration. Prior to this study, data related to the safety and efficacy of switching liver transplant patients from the reference MMF to the recently available generic formulation had not been reported.

In this study, the impact of generic substitution of MMF on indices of liver function was investigated in clinically stable liver transplant recipients. Also investigated was the impact of the use of the generic version of MMF on general and GI-specific HRQoL in the study population after medication conversion.

Maintenance of immunosuppressive balance is critical for allograft patency and minimization of adverse effects, and is ultimately implicated in the long-term survival of solid organ transplant recipients [14]. The degree of immunosuppression required to prevent allograft rejection is substantial in many patients, particularly in the immediate posttransplantation period. Moreover, a change in the immunosuppressive drug

could predispose patients to episodes of toxicity, infection, or allograft rejection [15].

In this study, two cases (1.4%) of acute rejection were reported, with no reports of severe GI intolerance, life-threatening infection, graft loss or death. Patients showed only slight changes from baseline in the questionnaires that were used; neither GSRS nor GIQLI score varied significantly after conversion. Furthermore, OTE evaluated by physicians and patients remained about the same. Because stable patients reported considerably better overall well-being at baseline in the evaluation questionnaires, changes in this group were not expected to be as pronounced as in patients suffering from generic drug conversion. The conversion from the brand-name MMF formulation to a generic MMF formulation at equimolar doses seemed to provide clinically effective immunosuppressant management for maintenance of liver transplant recipients, and the results supported existing data on similar efficacy maintained in other patients. Thus, we conclude that conversion from the brand-name MMF formulation to a generic MMF formulation was safe and well-tolerated, without causing GI complaints in patients.

Substitution of brand-name MMF for generic MMF (Myrept) in stable liver transplant recipients resulted in similar safety, GI complications, adverse effects, and quality of life as before conversion from the brand-name MMF product (Cellcept). Generic drugs can have the same therapeutic efficacy at a substantially lower price than brand-name drugs and are important for controlling healthcare costs. The use of generic immunosuppressive drugs could therefore generate significant cost savings in the long-term treatment of transplant recipients [8]. Generic immunosuppressants can be safely used as long as two main requirements are met: patients must consistently receive the same product, and patients and providers must be aware of transition points. Thus, outcomes research in generic immunosuppression is critically needed to assess the clinical and therapeutic equivalence of new generic immunosuppression formulations. In addition, pharmacoeconomic analyses of the transition from innovator to generic, and generic to generic formulations are needed. Currently, the true cost of generic substitution for solid organ transplant recipients is not known. Appropriate clinical decisions about the use of generic drugs must balance therapeutic outcomes, patient quality of life, and associated financial burden.

This study had several limitations. First, it lacked a control group so statistical comparisons of patients remaining on the brand-name formulation with patients switched to the generic formulation could not be performed. As a result, the data were descriptive and the analysis was exploratory. Conclusions from this study are observational and should only be compared to results from randomized control trials performed around the same time. Nevertheless, the observations of this study are clinically important and relevant to clinicians in Korea because data on generic MMF are relatively scarce. Second, the study population was outpatients, and compliance with the MMF regimen was not directly assessed. Third, long-term follow-up data are lacking.

In conclusion, this study demonstrated that, in maintenance liver transplant patients, generic MMF was a safe and effective alternative to brand-name MMF.

CONFLICTS OF INTEREST

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