The Cost of Gastrointestinal Adverse Events and the Impact of Dose-Reductions/Discontinuations on Acute Rejection in Kidney Transplant Patients of Mycophenolate Mofetil–Related Compared to Enteric-Coated Mycophenolate Sodium: A Pharmacoeconomic Study

G. Martinez-Mier[a,*] and A. Salazar-Ramirez[b]

[a]Department of Organ Transplantation, Instituto Mexicano del Seguro Social, Unidades Medicas de Alta Especialidad, Veracruz, Mexico; and [b]Health Economics & Outcomes Research Manager, Novartis Mexico, Mexico D.F., Mexico

ABSTRACT

Background. Mycophenolate mofetil (MMF) is effective in decreasing rejection and graft loss in renal transplant patients. Enteric-coated mycophenolate sodium (EC-MPS) was designed to reduce MMF gastrointestinal (GI) effects. Dose manipulations in MMF/EC-MPS produce GI tolerability, increasing the risk of rejection. Significant differences in tolerance of MMF/EC-MPS may have economic influence in transplant efficacy outcomes. Herein, we performed a pharmacoeconomic evaluation of acute rejection incidence and interventions in GI-intolerant patients using MMF/EC-MPS.

Methods. A cost-effectiveness analysis was performed through a decision tree model with a 1-year time horizon estimating costs and effectiveness of MMF and EC-MPS in renal transplant patients with GI intolerance. The costs and use of resources (US dollars; USD) were from payer perspective (Mexican Social Security). Primary health outcomes were mean cost of acute rejection and GI adverse events treatment. A probabilistic sensitivity analysis (PSA) was generated to test robustness of the model.

Results. Calculated incidence of MMF GI intolerance was 44%, and calculated rejection incidence for MMF was 24.05%. Calculated incidence of EC-MPS GI intolerance was 29%, and calculated rejection incidence for EC-MPS was 20.1% Total cost of MMF with GI intolerance during 1-year period plus cost of treating one rejection sums $752,107.25 USD. Total cost of EC-MPS with GI intolerance plus cost of treating one rejection sums $638,018.97 USD.

Conclusion. EC-MPS–based treatment is a cost-saving alternative vs MMF in GI-intolerant kidney transplant patients. PSA supports the decision to utilize EC-MPS based on cost-effectiveness analysis.

MYCOPHENOLIC ACID (MPA) has proved to be a very useful tool in immunosuppressive regimens since it was introduced around 1995. Mycophenolate mofetil (MMF), a formulation of MPA, is shown to be effective in decreasing incidences of acute rejection and short-/long-term graft loss in comparison against placebo and azathriopine with an acceptable safety profile in renal transplant patients [1–3]. Nonetheless, MMF gastrointestinal (GI) adverse events have been reported in up to 45% of patients [2,3], and these complications may lead to decreased medication compliance affecting graft and patient survival.

Enteric-coated mycophenolate sodium (EC-MPS) was designed to reduce the MPA-related GI effects seen with MMF [4]. EC-MPS (720 mg) has shown to be bioequivalent to 1000 mg MMF when evaluating MPA exposure and pharmacodynamic response of inosine monophosphate dehydrogenase [5]. Multiple studies suggest that EC-MPS

*Address correspondence to Gustavo Martinez-Mier, MD, Corporativo San Gabriel, Alacio Perez 928-314 Zaragoza, Veracruz 91910, Mexico. E-mail: gmtzmier@gmail.com

0041-1345/16
http://dx.doi.org/10.1016/j.transproceed.2016.02.017

confers significant improvement in GI symptoms in patients converted from MMF [6–9].

Dose manipulations to limit MPA exposure have been commonly used in the MMF and EC-MPS transplant population. By decreasing the MPA exposure, tolerability may be gained at the expense of an increased risk for rejection and graft loss [10,11]. MMF and EC-MPS intolerance have been reported in up to 45% to 65% and 42% of cases, respectively [12,13], and MPA intolerability in either MMF and/or EC-MPS leads to a recognized MMF dose reduction ranging from 7% to 74.4% [12,14–17]. Despite MPA dose reduction, MPA intolerance may be severe enough to result in a significant MPA discontinuation rate of 5% to 33% in MMF and 10% to 27.9% in EC-MPS patients [14,17]. Discontinuation may result in immunosuppression regimen changes, such as azathioprine use instead of either MMF or EC-MPS.

Biopsy proven acute rejection (BPAR) and graft loss are the standard measure of initial efficacy after kidney transplantation. Different studies comparing MMF against EC-MPS in kidney transplant (KT) patients observed BPAR rates of 23% to 30% in MMF-treated patients compared to 14% to 22.5% in EC-MPS–treated patients [16,18–20]. A 6% graft loss in MMF treated patients has been reported as a 3.5% to 5% loss in EC-MPS [19,20]. In addition, graft loss is adversely influenced by a 50% MMF dose reduction [13].

EC-MPS is recognized to be more expensive than MMF in most of the world including Mexico. However, although they have different prices, the significant differences in terms of their tolerance may have an economic influence in the total sum of the transplant patient's care once transplant efficacy outcomes are examined. In 2014, 2610 KTs were performed in Mexico; of these, 1422 (55%) were performed at the Mexican Institute of Social Security [21], making Mexican Social Security the principal immunosuppression care giver in the country. For that reason, we intended to perform a pharmacoeconomic evaluation of an efficacy outcome (BPAR) and their interventions (diagnosis, medications, and treatment) in GI-intolerant patients under MMF or EC-MPS immunosuppression from a Mexican perspective utilizing Mexican Social Security costs.

METHODS

The cost-effectiveness analysis used a decision tree analytic model with a 1-year time horizon. The analysis was used to estimate the costs and effectiveness of MMF and EC-MPS in renal transplant patients who develop either MMF and/or EC- MPS intolerance due to GI adverse events. The model structure was produced by studies addressing intolerance by the use of MMF and/or EC-MPS. The primary health outcome was mean cost of BPAR and GI adverse events treatment in GI-intolerant patients with MMF compared to EC-MPS.

Decision Tree Analytic Model

The transplant patient's care progression starts with MMF and/or EC-MPS immunosuppressive regimens. Initial MMF/EC-MPS GI intolerance was estimated to start 3 months after transplantation. The percentage of patients who develop GI intolerance was calculated by obtaining a mean average of GI intolerance from previously reported articles with MMF regimens [9,11–13] and EC-MPS regimens [9,12,13]. Patients with MMF and/or EC-MPS GI intolerance were further divided into 3 groups: patients with MMF/EC-MPS dose reduction, MMF/EC-MPS discontinuation, and patients remaining in full-dose regimens with supplementary treatment for GI adverse events. Patients with MMF/EC-MPS discontinuation were considered to use azathioprine as an antimetabolite drug for immunosuppression instead of MMF/EC-MPS. The percentage of patients with dose reduction, discontinuation, or full-dose regimens with GI adverse events treatment was calculated by obtaining a mean average from previously reported MMF regimens [9–12,14–18,20] and EC-MPS regimens [9,12,14–18,20] as well. The decision-tree model was only followed in patients who remained in either MMF or EC-MPS with dose reduction or full dose with supplementary treatment for GI adverse events. A BPAR incidence was calculated by same methodology previously described (mean average of previously reported articles) in MMF regimens [10–12,16,17,19,20] and EC-MPS regimens [12,16–20]. BPAR was further classified according to the Banff working classification of renal allograft pathology into acute cellular and antibody-mediated rejection [22]. BPAR diagnostic workup, type occurrence (acute cellular and/or antibody mediated), and proper BPAR treatment were determined by previously published managements with 1 or more of the following: intravenous (IV) steroids, antibody therapy, IV immunoglobulin, and plasmapheresis accordingly [23–26].

Model Inputs

MMF, EC-MPS, and azathrioprine costs were obtained from 2014 tender prices for the Institute of Mexican Social Security (IMSS) reported in their web page (COMPRANET) [27] (Table 1). A 45% increased cost was added to the decision-tree model for patients who experienced GI intolerance due to adverse events and received supplementary GI treatment based on previously published reports of GI adverse events cost of treatment [11,28–31]. BPAR workup and treatment costs were obtained by unitary cost of medical attention by Mexican Social Security [32]. Costs were obtained in Mexican pesos (MXN) and then converted to US dollars at a rate of $15 MXN for $1 US.

BPAR Diagnostic Work-up and Treatment

According to standard of care, the following studies were considered in the BPAR diagnostic workup: complete blood count, blood chemistry, calcineurin inhibitor serum through levels, urine analysis (urine sediment included), urine culture, fractional excretion of sodium, renal Doppler ultrasound, and kidney allograft biopsy [26].

A 3-day course of 500 mg IV methylprednisolone was considered initial treatment for steroid-sensitive acute cellular rejection [23–25]. When antibody was thought for acute cellular rejection treatment, thymoglobulin (1–1.5 mg/kg/day IV for 5 to 10 days) was considered standard of treatment [23–26]. Plasmapheresis (5 sessions), IV immunoglobulin (100 mg/kg), and rituximab (500 mg IV) were defined as treatment for antibody-mediated rejection [23,24,26]. Premedication with diphenhydramine, hydrocortisone, and acetaminophen for thymoglobulin, IV immunoglobulin, and rituximab was included as part of rejection treatment. Infectious prophylaxis after rejection treatments also was included in the analysis: thrimethropim-sulfametoxazole for steroid-treated acute cellular rejection and thrimetropim-sulfametoxazole, valganciclovir, and fluconazole for either antibody-treated cellular rejection or antibody rejection treated with plasmapheresis, IV immunoglobulin, and rituximab according to KDIGO clinical practice guideline