The Role of Generics in Kidney Transplant: Mycophenolate Mofetil 500 Versus Mycophenolate: 2-Year Results

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Abstract

Objectives: **The introduction of mycophenolate mofetil has proven itself effective in preventing acute rejection in renal transplant recipients. However, this cost is ineffective with countries with a limited income. This study sought to compare the clinical and therapeutic profiles of a generic formulation with mycophenolate mofetil.**

Materials and Methods: **This 2-year, single-center, prospective, randomized, open-label study investigated the efficacy and safety of a new mycophenolate mofetil generic formulation compared with mycophenolate renal transplant recipients.**

The study divided patients in 2 groups: 8 patients in G1 received mycophenolate mofetil 500 and 10 patients in G2 received mycophenolate. Their demographics were similar: mean age, 36.6±7.1 and 33.3±11.7 years; sex M/F: 2/6 and 5/5; mean donor age, 42.6±11.1 and 43.6±13.9 years; mean HLA mismatches, 2.7±1.2 and 3.3±1.5; deceased donors, 25% and 20%; and warm ischemia time, 40.2±11.9 and 38.7±10.5 minutes. All patients received 2 g daily of mycophenolate mofetil 500 or mycophenolate with initial dosage of 0.1 mg/kg/d and prednisolone.

Results: **One patient of 7 in the mycophenolate mofetil group and 4 of 6 in the mycophenolate group had 1 episode of acute tubular necrosis, and 1 patient in each group had an acute rejection with no significant differences between the groups. The area under the curve of the mycophenolate mofetil did not show any difference between the 2 groups. The values of serum creatinine were also comparable. Patient survival rate at 6, 12, and 24 months was 100% in the groups. The frequencies of digestive and hematologic adverse effects were comparable in the groups with no significant differences.**

Conclusions: **Use of mycophenolate mofetil 500 provided safe and effective immunosuppressive therapy compared with mycophenolate. However, as the duration of the study was short, these results need to be confirmed in a long-term study.**

Key words: *Acute rejection, Survival*

At the end of the twentieth century, transplant results with were mycophenolate mofetil showed it to be an established drug in the immunosuppressive armamentarium (1). Earlier studies have shown a significant decrease in 6 months; the incidence of rejection when mycophenolate mofetil was added to a calcineurin-based inhibitor, immunosuppressive protocol (2-3). However, owing to the cost of the drug, many transplant centers have elected short-term use (4).

The keen interest of third-party payers and the health authorities to reduce the high health care budget have made it necessary to introduce mycophenolate mofetil generics into the field of transplantation (5).

By definition, a product identified by its official chemical name rather than an advertised brand name is called a generic. If a drug exerts its pharmacologic effects at the same site, has the same potency, comes in the same dosage form, and has the same bioavailability as the brand name, it is considered a generic. The manufacturer is required to show that

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the generic drug is safe, tolerable, effective, and bioequivalent the pioneer drug. In Tunisia, mycophenolate mofetil generic, manufactured by Medis Laboratory, has been used in our kidney transplant center since January 2007.

The objective of this study was to compare the clinical and therapeutic profiles of a generic formulation with the innovator, mycophenolate mofetil.

Materials and Methods

We made a single-center, prospective, randomized, open-label study.

This study included all kidney transplant recipients who were operated between January 2007 and December 2008 at our institution. All patients received immunosuppression from day 0 with tacrolimus, mycophenolate mofetil, and methyl-prednisolone.

Tacrolimus was administered at 0.1 mg/kg/d initially, and then adjusted to achieve target trough levels of 8 to 3 ng/mL for the first 3 months and then of 5 to 10 ng/mL thereafter.

Mycophenolate mofetil was prescribed at a dosage of 2000 mg daily.

The reference drug contained 500 mg of mycophenolate mofetil (Cellcept 500) manufactured by Hoffmann-La Roche Switzerland. The tested drug was mycophenolate mofetil 500, (500 mg tablets; containing 500 mg of mycophenolate mofetil) developed by Medis, Tunisia.

Patients were divided into 2 groups: G1 was composed of 10 patients treated with Cellcept, and G2 was composed of 8 patients treated with mycophenolate mofetil 500.

The 2 groups were comparable concerning the average age, sex, frequency of live donors, mean duration of warm ischemia, and the frequency of HLA identities.

The principal analyzed parameter was the rate of acute rejection. Other parameters were acute tubular necrosis, serum creatinine rate, leucocytes, aspartate aminotransferase, alanine aminotransferase, actuarial patient, and graft survival at 6 months, 1 and 2 years, and adverse effects.

The pharmacokinetic profiles included C_{max}, serum concentration-time curve (AUC O-t), and T_{max}. C_{max} maximal measured plasma concentration after each treatment; AUC O-t was the area under the plasma concentration versus time curve from time zero to the last measurable time point as calculated by linear trapezoidal method.

Plasma was isolated to determine mycophenolate acid concentrations using high-pressure liquid chromatography with UV detector (HPLC-UV). Blood samples were collected predose, and then at T0, T 20 min, T 1 hour, and T 3 hours after dosage. These 4 points were used to construct the area under the curve (AUC).

The AUC was analyzed for the 2 groups at days (D) D0, D7, D30, D90, and D180. An AUC target for mycophenolate mofetil of 40 ng/mL/h was retained. T_{max} was the time that maximum plasma concentration was measured.

If the maximum value occurred at more than 1 time point, T_{max} was defined as the first time point with this value.

Results

The characteristics of the study population are shown in Table 1.

Table 1. Characteristics of the study population.

Group	Mycophenolate mofetil 500	Mycophenolate	*P*
Number of patients	8	10	NS
Mean age ± SD (y)	36.6 ± 7.1	33.3 ± 11.7	NS
Sex (women/men)	2/6	5/5	NS
Mean age of donor ± SD (y)	42.6 ± 11.1	43.6 ± 13.9	NS
Peritoneal dialysis/hemodialysis	3/5	3/7	NS
Warm ischemia time ± SD (min)	40.2 ± 11.9	38.7 ± 10.5	NS
Mean of HLA identities	2.7 ± 1.2	3.3 ± 1.5	NS
Deceased donors (%)	**25**	**20**	**NS**
Acute rejection delay (d)	30	7	NS
Dialysis duration (mo)	28.2 ± 1.4	36.4 ± 22.1	NS
Cytotoxic antibody before KT (%)	0	10	NS
Cytotoxic antibody after KT (%)	0	20	NS

Abbreviations: HLA, human leukocyte antigen; KT, kidney transplant; SD, standard deviation

The principal parameter tested was acute rejection, similar for both mycophenolate mofetil and Cellcept groups (Figure 1).

The incidence of acute tubular necrosis and the average serum creatinine levels were also similar for the 2 groups (Figures 2 and 3). The AUC was similar at day 7, day 14, month 1, and month 3 (Figure 4).

Patient and graft survivals at 6 months and 1 and 2 years were 100% for both groups (Table 2). The incidence of adverse effects is represented in Table 3. We did not find any significant differences between the groups concerning the studied parameters.

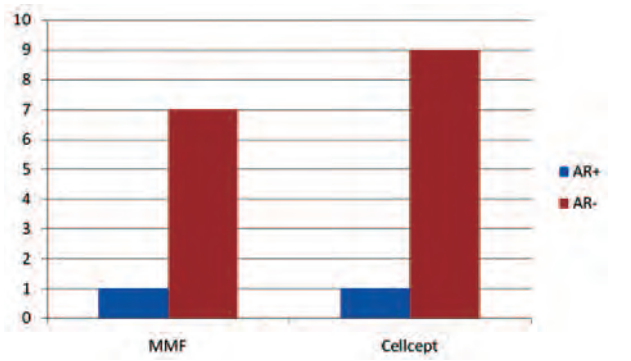

Figure 1. Number of patients with acute rejection.

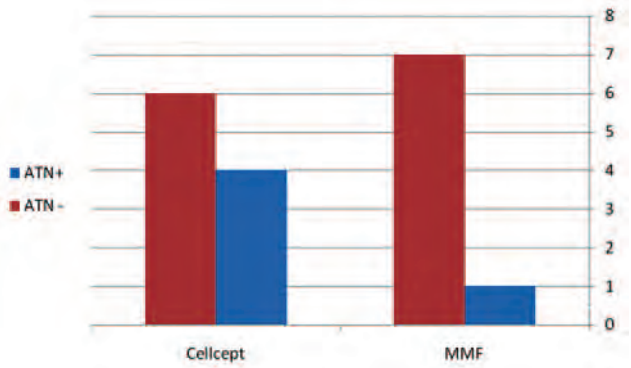

Figure 2. Number of patients with tubular necrosis.

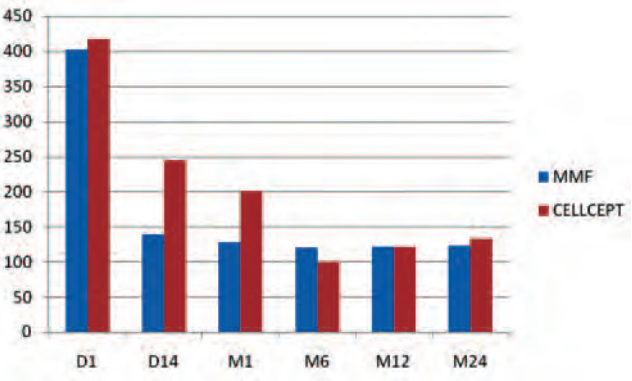

Figure 3. Average of serum creatinine (μmol/L).

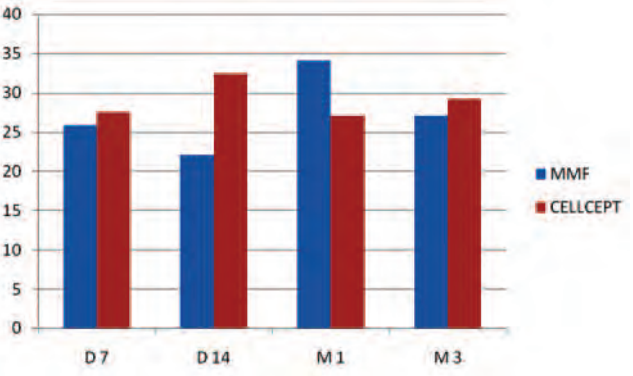

Figure 4. Area under the curve for the 2 groups (ng/mL/h).

Table 2. Patient and graft survivals.

Survival rate	Mycophenolate mofetil	Mycophenolate
0	100%	100%
Month 6	100%	100%
1 year	100%	100%
2 years	100%	100%

Table 3. Incidence of adverse effects.

	G1	G2	*P*
Leukocyte/mm^3 at day 7	6390 ± 1822	4850 ± 1062	NS
Infectious episodes	14	9	NS
Diarrhea	4	5	NS
Abdominal pain	2	0	NS
Elevated liver enzymes (AST-ALT)	0	0	NS

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Discussion

The history of generic drugs is somewhat checkered in the United States. Neither law nor regulation contains a definition of a generic drug. So, a definition has been proposed by Dr. Roger Williams for use by the US Food and Drug Administration. The definition for a generic drug is a drug product that compares to the pioneer, reference drug product in dosage form, strength, route of administration, quality, and performance characteristics and in intended use (6).

According to the United States Congressional Budget Office, generic drugs save consumers an estimated USD $8 to USD $10 billion per year at retail pharmacies (7). Even more is saved when hospitals use generics. It is important for physicians and patients that strict guidelines for drug approval are followed. Generics currently account for more than 42% of the total number of prescriptions in the United States (8).

The keen interest in health authorities to reduce the high health care budget makes it necessary to introduce generics into the field of transplantation. Immunosuppression with the tacrolimus plus mycophenolate mofetil has been shown to achieve better graft survival, fewer episodes of biopsy-proven acute rejection, and better renal function at 3-year follow-up than cyclosporine plus mycophenolate mofetil therapy.

In clinics, use of generic products is widespread and now plays an important role in the available therapeutic armamentarium. This also applies to transplant medicine. Several drugs that represent the

cornerstone in the therapeutic management of transplant patients currently do have generic alternatives, including those belonging to antihypertensive and immunosuppressant classes (9). Specific requirements are that generic formulations have the same molecular entity and should be bioequivalent with the innovator's product.

Theoretically, the generic preparation would improve adherence to treatment for their lower cost in countries with no social insurance or with limited incomes (10).

In Tunisia, 2 generics of cyclosporine were used in immunosuppressive therapy with good results compared to the principal molecule (Consupren in March 2000 and Equoral in February 2004, both manufactured by Medis Tunisia).

Mycophenolate mofetil is currently being prescribed for lifelong use. Both studies (11, 12) have shown that addition of mycophenolate mofetil to cyclosporine-based immunosuppressive protocol produced a significant decrease in the incidence of rejection within 6 months.

Several studies suggest a relation between early graft rejection and long-term graft survival (13, 14). The cost of Cellcept is prohibitive; therefore, long-term use is difficult for countries with limited incomes (15).

Thus, we compared the effect of a new mycophenolate mofetil generic formulation (mycophenolate mofetil 500 developed by Medis Tunisia in February 2006 and used in our department in January 2007) and Cellcept (Hoffman, La Roche) in adult transplanted patient.

We found no significant differences between the groups regarding the incidence of acute tubular necrosis and acute rejection. The AUC at D7, D14, D30, and D90 was comparable between the groups. Serum creatinine on day 14, and on the first, sixth, and 12th months was comparable between the 2 groups without a statistically significant difference. Patient survival at 6 months, and 1 and 2 years is comparable in both groups in 100% of the cases. The infectious episodes are more frequent in the Cellcept group (14 vs 9), but this difference was not significant.

Digestive problems (diarrhea and abdominal pain) were comparable in both groups. We did not notice any hematologic disorders in either group. These results prove the efficacy, safety, and tolerability of mycophenolate mofetil 500 to Cellcept at short and medium follow-ups. A long-term, follow-up is desirable to confirm these results.

Our findings correlate with a report by some authors. Masri and associates compared a generic of mycophenolate mofetil (TM-mycophenolate mofetil) and Cellcept concerning 3 parameters: AUC, C_{max}, and T_{max}, and they showed no significant difference at any time point (15).

Videla and associates compared the pharmacokinetic profiles of a generic formulation with the innovator mycophenolate mofetil, and showed that renal function at 12 months remained stable after conversion, and concluded that conversion to generic mycophenolate mofetil in stable renal transplant recipients showed good clinical results (10).

Finally, many questions must be answered regarding the timing and mechanism for the introduction of generics, especially in the Middle East Society for Organ Transplantation (MESOT) countries. There is an urgent need to create similar inspectors for the US Food and Drug Administration. This body should then establish criteria for quality and safety of the generics in our area (8).

Conclusions

We support the use of generic drugs in clinical practice. Certainly, this strategy will help increase access to essential medicine, particularly in emerging countries, that have limited resources to afford the cost of innovator products.

We showed similar results between generic mycophenolate mofetil and the pioneer drug. Longer duration of study and a larger numbers of patients are needed to draw definitive conclusions.

References

1. Djamali A, Premasathian N, Pirsch JD. Outcomes in kidney transplantation. Semin Nephrol. 2003;23(3):306-316.
2. Kim SJ, Huh KH, Han DJ, Moon IS, Kim SJ, Kim YL, et al. A 6-month, multicenter, single-arm pilot study to evaluate the efficacy and safety of generic tacrolimus (TacroBell) after primary renal transplantation. Transplant Proc. 2009;41(5):1671-1674.
3. Grinyo JM, Gil-Vernet S, Serón D, Cruzado JM, Moreso F, Fulladosa X, et al. Steroid withdrawal in mycophenolate mofetil-treated renal allograft recipients. Transplantation. 1997;63(11):1688-1690.
4. Stephan A, Barbari A, Kamel G, Aoun S, Masri MA. A one-center experience with a short course of mycophenolic acid. Transplant Proc. 1999;31(8):3289-3290.
5. Masri MA, Rizk S, Attia ML, Barbouch H, Rost M. Bioavailability of a new generic formulation of mycophenolate mofetil MMF 500 versus CellCept in healthy adult volunteers. Transplant Proc. 2007;39(4):1233-1236.

6. Meyer GF. History and regulatory issues of generic drugs. Transplant Proc. 1999;31(suppl 3A):10S-12S.
7. Masri MA, Haberal M, Rizvi A, Stephan A, Bilgin N, Naqvi A, et al. Switchability of neoral and equoral according to Food and Drug Administration rules and regulations. Transplant Proc. 2005;37(7):2988-2993.
8. Masri M. The generics in transplantation and the rules on their use. Exp Clin Transplant. 2003;1(1):65-68.
9. Müller H, Solari S, Zuñiga C, Pedreros C, Troncoso J, Morente C, et al. Immunosuppression with generic tacrolimus and mycophenolate mofetil in renal transplant recipients: preliminary report in Chile. Transplant Proc. 2008;40(3):705-707.
10. Videla C, Godoy C. Converting to a generic formulation of mycophenolate mofetil in stable kidney transplant recipients: 1 year of drug surveillance and outcome. Transplant Proc. 2007;39(3):602-605.
11. [No authors listed]. Placebo-controlled study of mycophenolate mofetil combined with cyclosporin and corticosteroids for prevention of acute rejection. European Mycophenolate Mofetil Cooperative Study Group. Lancet. 1995;345(8961):1321-1325.
12. Houde I, Isenring P, Boucher D, Noël R, Lachanche JG. Mycophenolate mofetil, an alternative to cyclosporine A for long-term immunosuppression in kidney transplantation? Transplantation. 2000;70(8):1251-1253.
13. Hall B, Surany M. Handbook of Transplant Immunology. New York; Medsci Publications; 1995:13.
14. Stephan AG, Barbari A, Masri M, Kamel G, Barakat Khoury W, Karam A, et al. A two-year study of the new cyclosporine formulation Consupren in de novo renal transplant patients. Transplant Proc. 1998;30(7):3563-3564.
15. Masri MA, Andrysek T, Rizk S, Matha V. The role of generics in transplantation: TM-MMF versus Cellcept in healthy volunteers. Transplant Proc. 2004;36(1):84-85.