Clinical Outcomes After Conversion From Brand-Name Tacrolimus (Prograf) to a Generic Formulation In Renal Transplant Recipients
A Retrospective Cohort Study

Kwaku Marfo, PharmD, MPH, BCPS; Samuel Aitken, PharmD; and Enver Akalin, MD

INTRODUCTION
Tacrolimus (Prograf, Astellas Pharma US) is a potent immunosuppressive medication that is recommended as a first-line agent in many renal transplantation protocols. Although it is better tolerated and slightly more effective than its predecessor, cyclosporine, tacrolimus is associated with a narrow therapeutic index and routine drug monitoring is required to ensure its effectiveness and to limit toxicities. Tacrolimus was first approved in 1994.

In August 2009, the first generic formulation of tacrolimus (made by Sandoz, a division of Novartis) became available. Generic medications, as defined in the Hatch–Waxman Act of 1984, accounted for approximately 70% of all prescriptions dispensed in the U.S. by 2010. Cost savings associated with generics are substantial; large-scale generic substitution has the potential to save approximately $229 million per year in Medicaid expenditures, or $2.8 billion for overall outpatient drug costs.

To gain marketing approval for a generic drug, a manufacturer first must prove bioequivalence in the rate and extent of absorption. This is typically accomplished through a small-scale in vivo study of healthy volunteers. In such studies, the maximum plasma concentration (C_max), which determines the rate of absorption, and the area-under-the-concentration (AUC) time curve, which assesses the extent of absorption, must have a geometric mean of generic-to-brand C_max and an AUC ratio with a 90% confidence interval (CI) from 80% to 125%.

Despite FDA standards, many clinicians have been reluctant to substitute generic drugs for branded products, especially those with a narrow range between efficacy and safety (e.g., such as tacrolimus with its narrow therapeutic index). Results with generic versions of cyclosporine (a counterpart to tacrolimus) have been conflicting, with some studies asserting that generic cyclosporine products are indeed detectably different from the brand-name equivalent and other studies finding no clinical differences between products. Because of this equivocal evidence, both the National Kidney Foundation and American Society of Transplant Surgeons released position statements arguing against the routine use of generic immunosuppressant agents without more rigorous in vivo data.

Data for the clinical use of generic tacrolimus are limited. In vitro studies comparing various non-U.S. brands of tacrolimus have shown that dissolution rates may vary among formulations, whereas prospective in vivo trials involving generic products that are unavailable in the U.S. have shown outcomes equivalent to those with historical controls. Retrospective case series completed in the U.S. have shown a small but significant drop in tacrolimus concentrations for the Reference Listed Drug and the generic drug (Sandoz), respectively, as follows:

- In the liver transplant recipients, the mean tacrolimus/dose ratio was 184.1 vs. 154.7 ([ng/mL]/[mg/kg per day]; P < 0.05).
- In the kidney transplant recipients, the mean tacrolimus/dose ratio was 125.3 vs. 110.4 ([ng/mL]/[mg/kg per day]; P < 0.05).

In this series, the drop in tacrolimus trough concentrations did not cause acute graft rejection or alter surrogate markers for liver and kidney function. In another U.S. multicenter experience with generic tacrolimus conversion, dose requirements and trough levels were similar when stable transplant recipients were switched from the brand-name to the generic medication on a milligram-to-milligram basis.

Both studies were performed in a controlled environment. The physicians were aware that generic substitution had occurred and were able to monitor patients to avoid consequences that might have developed as a result of the switch. Because laws regarding generic substitution vary among states, this model does not simulate a real-world scenario in which a patient, upon filling a prescription at a retail pharmacy, might be switched to a generic bioequivalent because of copayment policies or because of the availability of another product without the knowledge of the treating clinician.

In addition, the two U.S. studies did not account for the potential for conversion from one generic product to the other. Currently, five companies manufacturer generic tacrolimus in the U.S. (Accord Healthcare, Dr. Reddy Labs, Panacea Biotech Ltd., Sandoz, and Mylan); Sandoz also makes

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Dr. Marfo is Clinical Pharmacy Manager of Solid Organ Transplantation at Montefiore Medical Center–The University Hospital for Albert Einstein College of Medicine in Bronx, New York. At the time of this writing, Dr. Aitken was a pharmacy student at the University at Buffalo School of Pharmacy and Pharmaceutical Sciences in Buffalo, New York. He is currently an Infectious Disease Pharmacy Fellow at St. Luke’s Episcopal Hospital in Houston, Texas. Dr. Akalin is a Professor of Clinical Medicine in the Department of Medicine (Nephrology); Professor of Clinical Surgery in the Department of Surgery at Albert Einstein College of Medicine in Bronx; and Medical Director of the Kidney and Pancreas Transplant Program at Montefiore Medical Center in Bronx.
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A branded generic drug (Hecoria). It is fair to assume that if cost reductions and savings are the driving force for generic conversion, from the perspective of the payer and retail pharmacy, during periodic refills, it is possible that a patient might be switched from one generic product to another. Spence et al., in their clinical experience at Kaiser Permanente, reported average cost savings of $45 per month in drug-acquisition costs and savings of $26 per prescription copay when patients were switched from the brand-name product to the Sandoz generic tacrolimus formulation.

We hypothesized that there would be no difference in clinical outcomes when renal transplant patients were switched from brand-name tacrolimus (Prograf) to generic tacrolimus. We made our determinations on the basis of mean tacrolimus trough levels, serum creatinine levels, episodes of rejection, and complications following immunosuppression.

METHODS

We used a comprehensive electronic database (OTTR, Chronic Care Solutions), originally called the Organ Transplant Tracking Record. Using OTTR from an outpatient post-transplant clinic and a partnership with three specialty retail pharmacies, we retrospectively identified renal transplant recipients who had been switched from brand-name to generic tacrolimus (without notifying the treating clinician) between September 2009 and September 2010. Specialty retail pharmacies provided the refill history of all patients identified for inclusion in the study according to whether brand-name or generic tacrolimus was dispensed during the study period. We did not collect information about a specific manufacturer’s generic formulation that was dispensed at each refill; however, all three pharmacies stocked more than one generic formulation.

To limit our analysis to patients who were clinically stable with tacrolimus, we excluded all patients who were less than 3 months from their transplantation date at the time of conversion or for whom data were inadequate or incomplete. We analyzed the medical records of each patient from the three clinic visits immediately before the conversion and the three visits immediately after the conversion (i.e., 90 days before and after) using the date of the first dispensed generic prescription as an index for the converted patients.

For the controls, we selected all renal transplant patients receiving maintenance therapy with brand-name tacrolimus. We analyzed their medical records for three clinic visits before September 2009 and three clinic visits after September 2009 (i.e., 90 days before and after). We also collected information on tacrolimus 12-hour trough levels and serum creatinine.

All episodes of acute rejection and infection during the analysis period were recorded. For acute rejection episodes, we reviewed pathology records for biopsy results that were consistent with a diagnosis of organ rejection. (We typically perform biopsies for all patients with clinical suspicion of rejection.) For infectious complications, we reviewed medical records for clinical, microbiological, and diagnostic information that was consistent with bacterial infections (urinary tract infections, sepsis, pneumonia), viral infections, or fungal infections.

In addition to tacrolimus, our institution’s maintenance immunosuppression regimen consists of lifelong mycophenolate mofetil (CellCept, Genentech) 1,000 mg twice daily and prednisone 5 mg once daily. Azathioprine (e.g., Azasan, Salix) is substituted for patients who are intolerant of mycophenolate mofetil. Tacrolimus dosing is guided by target trough levels based on the time since the transplantation. During post-transplantation months 3 to 6, a trough level of 6 to 8 ng/mL is desired; beyond month 6, a trough level of 5 to 7 ng/mL is considered therapeutic. Trough levels are obtained once monthly for stable kidney transplant patients.

The study protocol was approved by our institution’s institutional review board.

STATISTICAL ANALYSIS

Paired Student t-tests were used to analyze pre-conversion and post-conversion laboratory values, such as 12-hour tacrolimus trough levels, serum creatinine levels, and blood glucose levels. We analyzed the incidence of acute rejection episodes and infectious complications before and after conversion using the chi-square test. Reported P values were two-sided, and P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

We performed a data analysis for 73 converted and 33 control patients who met all inclusion criteria. We excluded 25 converted and 18 control patients who were less than 3 months from their transplantation date; we also excluded patients if any of their laboratory results were missing. Baseline characteristics of 106 patients who met eligibility criteria are presented in Table 1. The median time from transplant surgery to generic conversion

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Converted Patients (n = 73)</th>
<th>Controls (n = 33)</th>
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<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>54 ± 13</td>
<td>51 ± 16</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>37 (50)</td>
<td>19 (58)</td>
</tr>
<tr>
<td>Ethnicity, % non-Caucasian transplant (No.)</td>
<td>52 (71)</td>
<td>22 (67)</td>
</tr>
<tr>
<td>Donor source, % deceased</td>
<td>55 (75)</td>
<td>24 (73)</td>
</tr>
<tr>
<td>Mean time to generic conversion from transplantation, days†</td>
<td>1,005 ± 1152</td>
<td>—</td>
</tr>
<tr>
<td>Previous history of acute rejection, %</td>
<td>3 (4)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concomitant immunosuppression regimen</th>
<th>Converted Patients (n = 73)</th>
<th>Controls (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC/MPA/PRED</td>
<td>60 (82)</td>
<td>25 (76)</td>
</tr>
<tr>
<td>TAC/AZA/PRED</td>
<td>3 (4)</td>
<td>—</td>
</tr>
<tr>
<td>TAC/MPA</td>
<td>—</td>
<td>2 (6)</td>
</tr>
<tr>
<td>TAC/PRED</td>
<td>10 (14)</td>
<td>6 (18)</td>
</tr>
</tbody>
</table>

*All P values > 0.05.
†Mean time to generic conversion from transplantation = the average time of post-transplant days before the patient was switched from brand-name to generic tacrolimus.

AZA = azathioprine; MPA = mycophenolic acid; PRED = prednisone; SD = standard deviation; TAC = tacrolimus.
was 719 days (range, 115–8,216 days).

All of the tacrolimus conversions were completed on a milligram-per-milligram basis without dosage adjustments for subtherapeutic or supratherapeutic levels. In the converted patients, mean 12-hour tacrolimus trough levels differed significantly between pre-conversion and post-conversion levels (6.8 ± 2.2 ng/mL vs. 6.0 ± 1.6 ng/mL, respectively; \( P = 0.0131 \)).

In the controls, the mean 12-hour tacrolimus trough levels before and after the index date were 7.9 ± 2.5 ng/mL and 7.0 ± 2.3 ng/mL, respectively; \( P = 0.1330 \)).

The mean 12-hour tacrolimus trough levels in both controls and converted patients at the different time points are depicted in Figure 1. There was a mean difference of 0.8 ng/mL in trough levels in converted patients compared with 0.9 ng/mL in controls. Concentrations differed at the various observation time points and between the two groups because of individual patient fluctuations in daily trough levels. In addition, the fact that all of the patients were at different time points since the transplantation procedure also contributed to the changes in trough levels observed.

The 12-hour tacrolimus target trough levels for dosage adjustments at our transplantation center are guided by the days since transplantation, as described previously (see page 485). Despite the differences, mean trough levels were within the desired therapeutic ranges for tacrolimus in both converted and control patients per our institution’s kidney transplant protocols with reference to time since transplantation. Mean serum creatinine levels before and after conversion were similar: 1.51 ± 0.55 mg/dL and 1.55 ± 0.66 mg/dL, respectively (\( P = 0.6914 \))

Mean serum creatinine levels in controls and in converted patients are shown in Figure 2. None of the patients experienced elevated serum creatinine levels greater than 0.5 mg/dL, which would have warranted a biopsy for a diagnosis of acute rejection.

At baseline, the number of acute rejection episodes was higher in converted patients than in controls. After a 1-year observation period, one patient from a group of 73 converted patients (1.4%) experienced an antibody-mediated rejection episode 130 days after being switched from branded to generic tacrolimus. This patient responded well to a total dose of
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2.0 g/kg of intravenous immune globulin (IVIG) and four sessions of plasmapheresis. However, his post-transplantation course was complicated by advanced hyperparathyroidism, and he underwent parathyroid surgery 150 days after transplantation. None of the controls experienced any rejection episodes during this observation period.

Blood glucose values in converted patients before the switch (128 ± 63 mg/dL) and after the switch (122 ± 60 mg/dL) did not differ significantly (P = 0.5566). Mean blood glucose levels in controls and in converted patients are shown in Figure 3.

In our review, we observed 10 documented pre-conversion infections and 12 post-conversion infections. In the pre-conversion period, there were six cases of urinary tract infections, two cases of bacteremia, and two cases of pneumonia. In the post-conversion period, there were nine cases of urinary tract infections, including two recurrent episodes, one case of bacteremia, and two cases of cytomegalovirus infections. We could not attribute the additional infectious complications to over-immunosuppression.

During the 1-year observation period, we observed no tacrolimus-related adverse events or toxicity.

DISCUSSION

We did not detect a discernible difference in the effectiveness and safety of generic tacrolimus when compared with the branded product. The differences that we observed in mean tacrolimus trough levels before and after conversion did not result in clinically relevant differences in graft function. Markers of drug toxicity or therapeutic failure were not profound after the conversion.

As for therapeutic failure, we assessed post-conversion increased episodes of graft rejection and serum creatinine levels. In a comparison of pre-conversion and post-conversion rates in control patients, neither outcome differed significantly. One episode of graft rejection was noted in a converted patient with advanced secondary renal hyperparathyroidism who subsequently underwent a parathyroidectomy.

Regarding drug toxicity, we evaluated the incidence of infectious complications, glucose abnormalities, and tacrolimus-related adverse effects. The fact that the number of infections tended to increase in the post-conversion period could not be attributed to the generic conversion, because we did not assess risk factors for infectious complications or the degree of over-immunosuppression.

STUDY STRENGTHS AND LIMITATIONS

One of the limitations of our study is its small sample size. Our short-term follow-up did not allow us to confidently assess whether an insignificant decline in the tacrolimus trough level was a result of the conversion to a generic formulation and whether such a decline could compromise graft outcomes in both the short and long term. We also realize the limitations of assessing these outcomes in a non-controlled trial.

Although the three clinic-visit laboratory assessments and the 1-year follow-up do not allow conclusions to be made about the long-term safety or effectiveness of generic tacrolimus, these results provide clinical data to confirm outcomes in renal function, acute rejection, glucose abnormalities, and infectious complications when patients are switched to the generic formulation. These endpoints represent data from clinical practice rather than from the standardized healthy volunteers used in bioequivalence studies.

One strength of our study was the average time from transplantation to generic conversion. Patients were, on average, more than 1 year from their transplantation date, a time period during which laboratory values and other clinical findings are likely to represent stable conditions, lending a high degree of external validity for interpreting our results. In addition, in this group of high-risk kidney transplant patients (i.e., consisting of a higher percentage of non-Caucasians), generic conversion did not compromise clinical outcomes. These results can be corroborated with findings from Spence et al., who, in their evaluation of clinical and safety outcomes associated with a conversion from brand-name to generic tacrolimus in transplant recipients, did not report adverse clinical events.

Our finding of a mean tacrolimus difference of 0.8 ng/mL before, versus after, conversion is similar to results from Momper et al.

Tacrolimus trough levels in our study and in the one by McDevitt et al. differed from those observed in other studies. McDevitt et al. and Spence et al. noted a 0.1-ng/mL and a 0.22-ng/ml increase, respectively, in tacrolimus trough levels after conversion. The McDevitt study took place at four transplant centers, where variations in reference ranges or assays used at the different laboratories to determine tacrolimus trough levels declined by an average of 0.87 ng/mL.

Trough tacrolimus levels in our study and in the one by McDevitt et al. differed from those observed in other studies. McDevitt et al. and Spence et al. noted a 0.1-ng/mL and a 0.22-ng/ml increase, respectively, in tacrolimus trough levels after conversion. The McDevitt study took place at four transplant centers, where variations in reference ranges or assays used at the different laboratories to determine tacrolimus trough levels would have had an influence on their overall analysis.

The patient population in Spence et al. was just as heterogeneous as that in the McDevitt study, because patients in the Kaiser Permanente Health Care System could have received a transplant from any of the 28 transplantation centers in California. The decline in post-conversion mean tacrolimus trough levels, compared with pre-conversion levels in our study and in that of Momper et al., corroborated with immunosuppression management in clinical practice, in which tacrolimus doses are adjusted to achieve reduced levels with an aging allograft.

Overall, these three studies support the hypothesis that similar tacrolimus trough levels can be achieved without compromised graft outcomes when stable transplant recipients are switched from brand-name tacrolimus to a generic formulation. However, these results do not eliminate the need to carefully monitor tacrolimus levels after conversion to the generic product in non-stable kidney transplant recipients. Because tacrolimus has a narrow therapeutic index and a high degree of inter-patient and intra-patient variability, routine monitoring should remain standard clinical practice.

In a more recent pharmacokinetic study conducted by Alloway et al., Sandoz’s generic tacrolimus formulation was bioequivalent to tacrolimus as the Reference Listed Drug in stable kidney transplant recipients. As was the case in our study, intravariability in tacrolimus trough levels was observed in that study’s pharmacokinetic assessments.
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COST

We did not evaluate the most important factor that drives generic substitution—cost savings. Any cost savings from the patient’s perspective would have been determined from the copayment at retail pharmacies. Most of our patients were Medicaid beneficiaries for whom copays are insignificant and are not routinely collected. McDevitt et al. found that when cost savings were assessed, there was a net monthly benefit of $23 in copays when transplant patients were switched from brand-name to generic tacrolimus.18 In addition to patients, third-party payers and retail pharmacies also benefit financially from generic substitution.

Spence et al. noted an average savings of $45 per month in drug-acquisition costs for Kaiser Permanente when transplant recipients were switched to generic tacrolimus.29 In addition to the therapeutic benefits and potential cost savings from generic substitution, there is a potential for increased medication adherence, especially if the cost of obtaining the medication is a limiting factor. We did not specifically address patient adherence; however, because all three specialty retail pharmacies, as a service to their customers, automatically refill patients’ prescriptions monthly without receiving calls from patients, we might have observed complete adherence using the medication refill history in both controls and converted patients.

CONCLUSION

Our results serve to dispel misconceptions that generic tacrolimus is an inherently inferior product to the brand-name product (Prograf). Additional studies to evaluate the long-term effect of graft function and patient adherence from generic tacrolimus conversion are warranted. Furthermore, a randomized controlled trial is required to assess tolerability (e.g., infectious complications, hyperglycemia leading to new-onset diabetes, malignancy, and cardiovascular disease as a result of over-immunosuppression from conversion of brand to generic tacrolimus).

In stable renal transplant recipients, generic tacrolimus did not confer negative clinical outcomes and it appeared to be safe and effective. Although routine monitoring is necessary, additional tacrolimus trough monitoring after generic conversion might not be warranted. However, collaboration with retail and specialty pharmacies is important to eliminate the potential for uncontrolled switching.

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REFERENCES