Generics: Are all immunosuppression agents created equally?

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Background. *The Affordable Care Act initiated innumerable cost-containment measures, including promoting generic conversion from brand medications and directing the Food and Drug Administration to decrease requirements for generic approvals. Despite this mandate, few data existed on generic conversion of immunosuppressant medications with narrow therapeutic troughs.*

Methods. *A retrospective analysis of our initial experience with generic tacrolimus (n = 39) was performed using a control cohort from our renal transplant database. A rejection and cost analysis was performed using a consecutive 2-year prior cohort (n = 159) as a control to determine the effect of generic conversion on tacrolimus a narrow therapeutic index immunosuppressant medication.*

Results. *During the first year after transplantation, the generic group had a greater drug variability (20% ± change in trough levels) that required more dosage adjustments (5.42 vs 3.59 drug dosage changes; P = .038) to obtain a stable dose, required increased number of intravenous magnesium infusions (4.95 vs 1.68 infusions; P = .001), and incurred a greater incidence of rejection (23.1% vs 10.2%; P = .024). A yearly institutional cost was evaluated against a negotiated $18,000/yearly central pharmacy cost savings compared with a $652,862 institutional cost to treat unanticipated rejections.*

Conclusion. *Programmatic conversion from brand to generic tacrolimus resulted in increased drug variability, a greater incidence of magnesium wasting, and more episodes of rejection, leading to increases in institutional costs of care. This government-driven attempt at cost containment may be applicable to noncritical medications such as antibiotics and antihypertensives, but this policy should be reconsidered for narrow therapeutic index medications, such as tacrolimus and other immunosuppressant medications. (Surgery 2015;158:1049-55.)*

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In 2010, president obama and the united states congress introduced the affordable care act. This legislature sought to reduce the cost of American health care. In the area of prescription medications, this legislature increased Medicaid's rebates on prescription medications, changed the Food and Drug Administration's (FDA) application process for generic drugs, and prescribed the conversion of brand medications to generics or generic equivalents when available. This abbreviated approval process now allows a generic application to be made shortly before the expiration of a brand name drug's patent and affords the approval of "biosimilar" or "interchangeable" products. Reference medications were provided a 12-year exclusivity period, whereas "biosimilar" products could be submitted for approval within 4 years of a reference medication's approval.[1,2]

FDA approval of generics is based on serum measurements of maximal drug concentration and area under the concentration time curves that fall within the 90% confidence interval of the reference medication with a bioequivalence limit of 80%–125%.[3-5] A typical bioequivalence study involves a single dose, and a 2-way crossover study in 24–58 healthy patients with the number of patients required based on established drug variability and food interactions. Generic approval is then granted on what the FDA considers a "high

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degree of similarity to a specific reference product as evidenced by analytical studies, animal studies and studies that show the safety, purity and potency in one or more appropriate 'conditions of use' for which the reference product is approved."[6,7]

Tacrolimus is a macrolide-derived immunosuppressant that acts as a calcineurin inhibitor, downregulating interleukin-2 production and T-cell function. The FDA first approved tacrolimus in 1984 for prophylaxis against rejection in liver transplant recipients. Tacrolimus subsequently was approved for recipients of kidney and heart transplants and constitutes the majority of the current calcineurin inhibitor usage worldwide. Patent protection for tacrolimus expired in April 2008; however, the FDA did not approve the first generic tacrolimus until August 2009.

Currently, there are 8 generic forms of tacrolimus approved by the FDA and in use in the United States. Unlike many other medications, tacrolimus is an immunosuppressant drug that has a narrow therapeutic index. Any wide trough variations resulting from alternative formulations or unanticipated interactions in solid-organ transplant recipients can be catastrophic. Because the FDA's only requirement is bioequivalence, there is a dearth of safety, efficacy, and therapeutic equivalence trials. Our current study seeks to examine the clinical efficacy of a single generic form of tacrolimus in a group of renal transplant recipients.

METHODS

Our study is a retrospective analysis of the clinical efficacy and institutional costs during the first year after transplantation for patients receiving "branded" generic tacrolimus compared with brand tacrolimus. In January 2013, our program was converted from brand to generic tacrolimus as a cost-savings initiative. This initiative provided a negotiated annual institutional cost savings of $18,000 per year for the central pharmacy budget. The comparison control group was created from patients who had been receiving brand tacrolimus (Astellas, Osaka, Japan). This group consisted of 159 renal allograft recipients who underwent transplantation from the period between January 2011 and December 2012. All pediatric and multiorgan transplants were excluded.

To minimize the potential variability between multiple available generics, we selected a "branded" generic to insure patient recognition and drug constancy. The study group that underwent transplantation during the first 2 quarters of 2013 then received "branded" generic tacrolimus (Bern, Switzerland). The integrity of the branded generic was insured by the use of only selected mail-order and outpatient pharmacies that carried and prescribed only branded generic as well as instructing our patients to bring their filled pill boxes to clinic to insure the branded generic drug was being taken. Data were collected and analyzed for the first-year post-transplant.

During this time period our immunosuppression regimen had been standardized for more than 3 years. Renal transplant recipients received alemtuzumab induction, 3 doses of steroids, tacrolimus (0.1 mg/kg/day) as our calcineurin inhibitor, and mycophenolic acid (720 mg twice a day). A standardized protocol was used to monitor drug levels with target trough levels. For the first 3 months after transplantation, the target trough level for tacrolimus was 10–12 ng/mL, in the second 3 months it was 8–10 ng/mL, and for months 6–12 months it was 6–8 ng/mL. A significant variation in FK (Prograf) level was defined as trough levels increasing or decreasing by more than 20% on a stable dose requiring dose alteration. Serial serum monitoring included creatinine, donor-specific antibody (DSA), cytomegalovirus, Epstein-Barr virus, and BK virus levels were performed at 3, 6, and 12 months. Any change from baseline serum creatinine level greater than 10–15% triggered hydration, FK level measurement and, if unresolved, a renal Doppler ultrasonography and percutaneous biopsy.

A positive DSA resulted in a percutaneous biopsy and a standardized antibody–mediated rejection treatment consisting of 5 sessions of plasmapheresis and treatment with rituxan (Genentech, San Francisco, CA) and velcade (Takeda, Osaka, Japan). In cases of hematologic or infectious complications, such as urinary tract infection, patients would receive intravenous immunoglobulin (CSL Bering, King of Prussia, Pennsylvania). Isolated T-cell rejections were diagnosed by percutaneous biopsy with the acute cellular rejection management dictated by histologic Banff classification. Borderline rejections were not considered as rejection in this study and were treated with increased tacrolimus. Banff 1 rejection was treated with a 3-day pulse of solumedrol and if steroid resistant would progress to thymoglobulin (Genzyme, Cambridge, MA). Banff 2 or greater was treated with 5–10 days of thymoglobulin. Mixed rejections (T-cell and antibody–mediated rejection) were treated with a combination of both therapies as dictated by biopsy. Magnesium wasting associated with tacrolimus was corrected with