Review Article

Generic tacrolimus in solid organ transplantation


Abstract: The availability of a wide range of immunosuppressive therapies has revolutionized the management of patients who have undergone solid organ transplantation (SOT). However, the cost of immunosuppressive drugs remains high. This situation has led to the development of generic equivalents, which are similar in quality, safety, and efficacy to their approved innovator drugs. There are data available for three generic brands, tacrolimus (Intas), tacrolimus (PharOS), and tacrolimus (Sandoz). Bioequivalence has been demonstrated for generic tacrolimus (Sandoz) within a narrow therapeutic range to its innovator tacrolimus drug (Prograf) in both healthy volunteers and kidney transplant patients. Clinical experience with this generic tacrolimus formulation has also been established in both de novo and conversion patients who have undergone kidney and liver transplantation, as well as in conversion of other SOT patients, including lung and heart recipients.

Solid organ transplantation (SOT) has been an area of rapid development over the last few decades and is the treatment of choice for many patients with end-stage organ failure of vital organs, including the kidney, liver, heart, and lungs. Five-yr patient survival rates for most organ transplant programs now exceed 50–70% (1). The introduction of immunosuppressants for the prevention and treatment of organ rejection has been fundamental in the establishment of SOT as a viable treatment option (2). SOT recipients typically receive lifelong treatment with immunosuppressive drugs, with the ultimate aim of prolonging patient and graft survival (2). Immunosuppression for SOT is commonly based on multiple drug regimens that often include an antiproliferative agent, a calcineurin inhibitor, and a period of steroid therapy. The classical calcineurin inhibitors, cyclosporine and tacrolimus, are used for prevention, maintenance, and reversal of established rejection (2, 3).

The financial costs of immunosuppressive therapy remain high. This situation has led to the development of generic equivalents, which are similar in quality, safety, and efficacy to their approved innovator drugs. Tacrolimus, cyclosporine, and...
This article summarizes the available published data for three generic tacrolimus brands, considering the bioequivalence and clinical experience reported in de novo and conversion patients who have undergone kidney, liver, and other SOTs. These generic tacrolimus formulations are immediate release, twice daily, oral preparations licensed for the prophylaxis of transplant rejection in liver, kidney, or heart allograft recipients, and the treatment of allograft rejection resistant to treatment with other immunosuppressive medicinal products (4–7).

Bioequivalence of generic tacrolimus with innovator drug

Licensing of generic drugs requires single-dose bioequivalence studies in healthy volunteers who typically receive the generic and innovator products in a two-way crossover study. The volunteers undergo blood testing throughout the dosing interval to facilitate the calculation of the mean maximal plasma concentration ($C_{\text{max}}$) and the mean area under the curve (AUC). AUC concentration measurements represent the extent of absorption. The $C_{\text{max}}$ and the time to $C_{\text{max}}$ ($t_{\text{max}}$) characterize the rate of this absorption. For the majority of generic products, bioequivalence is said to exist if the 90% confidence intervals for these values fall within the accepted range of 80–125%. The European Medicines Agency (EMA) has recommended a tighter acceptance margin of 90–111% for certain “critical dose drugs,” of which tacrolimus is one example (8).

In addition, there is no requirement to determine bioequivalence in the target population (i.e., transplant recipients) or to demonstrate efficacy, safety, or effects of commonly co-prescribed medications.

Although bioequivalence between a new generic product and the innovator product must be demonstrated, there is no requirement to show bioequivalence between the generic product and other generic formulations already in use. Switching between generic formulations should be undertaken in a planned fashion with appropriate monitoring and under the supervision of a transplant clinician (9).

Bioequivalence studies in healthy volunteers

Bioequivalence of generic tacrolimus (Sandoz) and innovator drug has been demonstrated in two open-label, single-dose, randomized, two period, two treatment, two sequence, two-way crossover studies carried out under fasted conditions in 46 healthy male subjects, aged 19–43 yr (10). In these studies, which assessed the 0.5 and 5 mg doses of tacrolimus (Sandoz), the 90% confidence intervals calculated for AUC$_{0\rightarrow\infty}$, AUC$_{0\rightarrow\infty}$, and $C_{\text{max}}$ were in agreement with those calculated by the marketing authorization holder and were within the bioequivalence acceptance range of 80–125% (Table 1). Based on the pharmacokinetic parameters of tacrolimus under fasting conditions, it was concluded that generic and innovator drugs were bioequivalent with respect to rate and extent of absorption, and fulfilled the bioequivalence requirements outlined in the relevant Committee for Medicinal Products for Human Use (CHMP) Note for Guidance. Bioequivalence for the 5-mg capsules proved to be within the narrow range recommended by the EMA. However, due to insufficient patient numbers in the study that investigated the 0.5 mg dose, the narrow therapeutic range was not reached. As a result, a new open-label, single-dose, randomized two treatment, two period, two sequence, two-way crossover bioequivalence study with an acceptance range of 90–111% was needed.

<table>
<thead>
<tr>
<th>Treatment (n = 43)</th>
<th>Dose (mg)</th>
<th>AUC$_{0\rightarrow\infty}$</th>
<th>AUC$_{0\rightarrow\infty}$</th>
<th>$C_{\text{max}}$</th>
<th>$t_{\text{max}}$</th>
<th>$t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>0.5</td>
<td>34.3 ± 18.6</td>
<td>37.2 ± 19.1</td>
<td>3.25 ± 1.19</td>
<td>1.25 (0.75–3.5)</td>
<td>36 ± 8</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>402 ± 211</td>
<td>424 ± 219</td>
<td>39.2 ± 13.5</td>
<td>1.5 (0.75–3.0)</td>
<td>34 ± 7</td>
</tr>
<tr>
<td>Reference</td>
<td>0.5</td>
<td>32.2 ± 19.6</td>
<td>35.5 ± 20.2</td>
<td>3.21 ± 1.27</td>
<td>1.5 (0.75–2.67)</td>
<td>35 ± 4</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>388 ± 207</td>
<td>410 ± 214</td>
<td>39.3 ± 14.5</td>
<td>1.75 (0.75–6.0)</td>
<td>36 ± 8</td>
</tr>
<tr>
<td>Ratio (90% CI)$^{b}$</td>
<td>0.5</td>
<td>1.10 (1.01–1.19)</td>
<td>1.06 (1.00–1.14)</td>
<td>1.03 (0.94–1.11)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>1.05 (0.99–1.11)</td>
<td>1.04 (0.99–1.10)</td>
<td>1.01 (0.92–1.11)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CV (%)</td>
<td>0.5</td>
<td>22.7</td>
<td>19.3</td>
<td>23.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>5.0</td>
<td>15.2</td>
<td>14.0</td>
<td>27.0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

AUC$_{0\rightarrow\infty}$, area under the plasma concentration–time curve from time zero to infinity; AUC$_{0\rightarrow t}$, area under the plasma concentration–time curve from time zero to t hours; $C_{\text{max}}$, maximum plasma concentration; $t_{\text{max}}$, time for maximum concentration; $t_{1/2}$, half-life; CV, coefficient of variation.

$^{a}$Non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ (median, range).

$^{b}$ln-transformed values.
performed in 219 healthy male subjects, aged 19–43 yr (10). This study confirmed that calculated 90% confidence intervals for AUC$_{0-\infty}$, AUC$_{inf}$ and $C_{max}$ for tacrolimus were within the predefined 90–111% acceptance range (Table 2).

Two other generic tacrolimus brands have been investigated for bioequivalence in healthy volunteers. The 90% CIs for generic tacrolimus (Intas) vs. innovator drug were 102.99–120.80% for $C_{max}$ and 91.5–105.9% for AUC$_{0-72}$ at the 0.5 mg dose; and 110.6–121.0% for $C_{max}$ and 96.2–103.6% for AUC$_{0-5}$, for the 5 mg dose (11). The 90% CIs for generic tacrolimus (PharOS) vs. innovator drug were 105.6–117.9% for $C_{max}$ and 93.06–104.74% for AUC$_{0-5}$ at the 5 mg dose (12).

Therefore, of the three generic products investigated, tacrolimus (Sandoz) is the only product to achieve the EMA requirement for both AUC and $C_{max}$.

Bioequivalence studies in transplant patients

Regulatory approval of generic products requires only the demonstration of bioequivalence with the innovator drug in healthy volunteers. However, kidney transplant recipients are known to exhibit a higher rate of tacrolimus clearance than healthy volunteers (13), and the need for robust pharmacokinetic data for the use of new generic formulations in this patient group has previously been highlighted (14, 15). In addition, both the USA (16) and European (9) transplant societies, as well as other expert groups (17, 18), have noted the limitations of extrapolating data from healthy volunteers to transplant populations.

Tacrolimus pharmacokinetics are characterized by a high degree of interpatient and to a lesser extent intrapatient variability. Factors affecting tacrolimus pharmacokinetics include patient demographics, liver function, diurnal variation, concomitant immunosuppressant administration, gastrointestinal disturbances, coexisting diabetes mellitus, and genetic differences in CYP3A4 and P-glycoprotein expression (19). In transplant patients, the key contributors to intrapatient variability in immunosuppressant dosing are usually drug–drug, drug–disease, and food–drug interactions (20).

A prospective, multicenter, open-label, randomized crossover study to compare the steady-state pharmacokinetics of generic tacrolimus (Sandoz) and innovator drug in stable kidney transplant patients was carried out by Alloway et al. (20). During a 14-d screening period, eligible patients continued to receive their current tacrolimus formulation at an unchanged dose. Following re-evaluation for inclusion/exclusion criteria, patients were then randomized to remain on their current tacrolimus preparation or to switch to the alternative formulation on a mg:mg basis. The primary objective of the study was to estimate the ratio of AUC$_{0-12}$ and $C_{max}$ at steady state for generic vs. innovator drug in stable kidney transplant patients using data from Day 14 and Day 28 of the study. A total of 71 patients were recruited to the study; 68 were evaluable for pharmacokinetics; and 65 completed the study. The mean (SD) tacrolimus dose at baseline was 5.7 (4.2) mg/d (median 4.0 mg/d, range 0.5–20.0 mg/d). All patients received an unchanged dose throughout the study, and all measured tacrolimus trough concentrations were above the lower limit of quantification (approximately 0.10 ng/mL). The drug concentration profiles for generic tacrolimus and innovator drug are shown in Fig. 1 (20). Importantly, there were no statistically significant differences in AUC$_{0-12}$, $C_{0}$, $C_{max}$, or $t_{max}$ between generic tacrolimus and innovator drug based on mean values of data obtained on Day 14 and Day 28. Correlations (r values) between $C_{12}$ and AUC$_{0-12}$ at Day 14 and Day 28 for generic tacrolimus and innovator drug were 0.837 and 0.917 vs. 0.773 and 0.887, respectively. Means of individual subject’s coefficient of variation values for AUC$_{0-12}$, $C_{max}$ and $C_{0}$ across all four pharmacokinetic assessments (Days 7, 14, 21, and 28) were similar for both treatment groups.

Table 2. Bioequivalence of generic tacrolimus 0.5 mg in the 90–111% range

<table>
<thead>
<tr>
<th>Treatment (n = 207)</th>
<th>AUC$_{0-\infty}$</th>
<th>AUC$_{inf}$</th>
<th>$C_{max}$</th>
<th>$t_{max}$</th>
<th>$t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>32.8 ± 16.7</td>
<td>41.0 ± 22.8</td>
<td>3.47 ± 1.35</td>
<td>1.5 (0.75–4.0)</td>
<td>36 ± 10</td>
</tr>
<tr>
<td>Reference</td>
<td>31.6 ± 16.4</td>
<td>39.8 ± 22.6</td>
<td>3.71 ± 1.39</td>
<td>1.5 (0.5–3.0)</td>
<td>37 ± 11</td>
</tr>
<tr>
<td>Ratio (90% CI)$^{b}$</td>
<td>1.05 (1.02–1.08)</td>
<td>1.04 (1.01–1.07)</td>
<td>0.93 (0.90–0.97)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CV (%)</td>
<td>19.2</td>
<td>20.3</td>
<td>22.0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

AUC$_{0-\infty}$, area under the plasma concentration–time curve from time zero to infinity; AUC$_{inf}$, area under the plasma concentration–time curve from time zero to $t$ hours; $C_{max}$, maximum plasma concentration; $t_{max}$, time for maximum concentration; $t_{1/2}$, half-life; CV, coefficient of variation.

$^{a}$Non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range).

$^{b}$In-transformed values.

Generic tacrolimus in SOT
Drug to achieve similar tacrolimus exposure (20). Generic/brand ratios and 90% CI intervals: Area under the curve (AUC) \(_{0-12 \text{ h}}\) 1.02 (90% CI 97–108%, \(p = 0.486\)); \(C_{\text{max}}\) 1.09 (90% CI 101–118%, \(p = 0.057\)); \(C_{\text{min}}\) 1.02 (90% CI 95–109%, \(p = 0.651\)). Application of bioequivalence testing to both the generic and the innovator drug, comparing the ratios of geometric means for AUC\(_{0-12 \text{ h}}\) and \(C_{\text{max}}\) at different time points one wk apart, illustrated that both formulations showed variability even within the same treatment period. The ratio of geometric means for both formulations varied between 0.96 and 1.06 at Day 7 vs. Day 14 and Day 21 vs. Day 28, but was not significantly different from each other. The study concluded that generic tacrolimus had a similar pharmacokinetic profile to innovator tacrolimus and was bioequivalent in kidney transplant recipients according to US Food and Drug Administration and EMA guidelines.

**Clinical evidence for de novo use**

A number of publications have reported the use of generic tacrolimus *de novo* in transplantation. All studies have so far used tacrolimus (Sandoz).

A transplant group in Utah compared the dose requirements of generic tacrolimus with innovator drug to achieve similar tacrolimus exposure \((C_0)\) over the first 28-d post-transplant (21). They took the first 40 kidney transplant patients treated with generic tacrolimus and compared them with the next 40 patients who received innovator drug. In the generic group, 33 patients met the inclusion criteria vs. 34 innovator drug-treated patients. Mean dose (mg/kg/d) and \(C_0\) were similar for all time points for both formulations, but renal function (glomerular filtration rate) assessed by Cockcroft-Gault was significantly higher with innovator drug at Day 28 (73 ± 29 vs. 67 ± 20 mL/min; \(p = 0.02\)). Other safety parameters were not included. The group concluded that initial dosing strategies were similar for both formulations as similar doses achieved comparable tacrolimus drug concentrations.

Driven by the opportunity to reduce costs, a UK transplant center introduced generic tacrolimus in place of the innovator drug in their *de novo* transplant program and subsequently sought to evaluate the relationship between \(C_0\) and AUC in a cohort of 16 patients (22). In the 13 patients who received donation after cardiac death organs and in whom induction was with basiliximab, generic tacrolimus was commenced at 0.1 mg/kg/d divided into two equal doses with target blood levels of 8–10 ng/mL. In the three patients who received living donor organs, induction was with alemtuzumab and generic tacrolimus administration at 2 mg twice daily was delayed until Day 3 post-transplantation with target blood levels of 5–7 ng/mL. Serial tacrolimus concentrations were measured on Day 4 or 5 (Day 5 in the three alemtuzumab patients) post-transplantation. Efficacy and safety were not reported. The linear regression coefficient of multiple determination \(\left[\hat{r}^2\right]\) for the relationship between \(C_0\) and the AUC was 0.92. Comparable to the best available data for the innovator drug, these results support the use of \(C_0\) as a reliable marker of AUC (total tacrolimus exposure) with generic tacrolimus.

The same center subsequently reported its clinical outcome data. A retrospective single-center clinical comparison of innovator drug \((n = 48)\) and generic tacrolimus \((n = 51)\) in *de novo* kidney transplant recipients found no statistically significant differences in the rates of patient survival, graft survival, biopsy-proven acute rejection, calcineurin inhibitor toxicity, cytomegalovirus infection, delayed graft function, and transplant function between the two comparable treatment groups at six months, indicating therapeutic equivalence (23). Heldenbrand et al. (24) compared the pharmacokinetics and clinical outcomes in 55 *de novo* kidney and liver transplant recipients administered either generic tacrolimus or innovator drug. The patient group comprised 34 kidney and 21 liver patients, of whom 16 kidney/11 liver patients were initiated on generic tacrolimus and 18 kidney/10 liver patients were started on innovator drug. Tacrolimus dose and whole blood levels were recorded at two wk and monthly for the first three months after transplantation. Outcomes were compared by combining kidney and liver patients for both formulations. Acute rejection occurred in 7% of patients for both formulations. Both tacrolimus mean dose and blood concentration were significantly higher with generic tacrolimus at two wk but were statistically similar by Month 3. No safety data were provided. It was
concluded that the ability to achieve and maintain therapeutic tacrolimus concentrations, and the incidence of rejection episodes were similar.

In the largest de novo experience in liver transplantation, Cheung et al. (25) described the outcome of 48 patients initiated on generic tacrolimus and compared this to 46 similar patients commenced on innovator drug. In this study, total tacrolimus doses and $C_0$ levels were similar in both groups, and there were no significant differences in the rates of biopsy-proven rejection, cytomegalovirus infection, acute kidney injury, sepsis, or graft loss between groups.

**Clinical evidence for conversion**

There is limited published experience for conversion of any branded immunosuppressive drug to a generic equivalent. However, a number of studies investigating the conversion of patients to generic tacrolimus (Sandoz) from its innovator drug have now been published. The results from these studies should be viewed in context as they are limited by the fact that they are largely non-randomized and non-placebo controlled and assess only one generic formulation.

**Kidney**

As has been discussed above, in the prospective, randomized, two period (14 d per period), crossover, and steady-state pharmacokinetic study undertaken by Alloway et al. (20), generic tacrolimus showed a similar pharmacokinetic profile to innovator tacrolimus (as assessed by a comparison of AUC$_{0-12\ h}$, $C_{\text{max}}$, and $C_0$ concentrations) in stable renal transplant patients. Clinical outcomes were also similar across the two groups. There were no graft losses or episodes of rejection during this short study. Eight patients (11.9%) experienced a total of nine adverse events (AEs) while receiving generic tacrolimus, compared to 12 patients (17.9%) who experienced 21 AEs during administration of the innovator drug. The only AE to occur in more than one patient under generic tacrolimus was oropharyngeal pain ($n = 2$). During treatment with innovator tacrolimus, vomiting ($n = 4$), nausea ($n = 2$), diarrhea, and headache ($n = 3$) occurred in more than one patient. No unexpected AEs were observed, and most AEs were mild and transient. One patient experienced three serious AEs (headache, mild rash, and squamous cell carcinoma) during treatment with the innovator drug. None were considered to be related to study drug.

In a study by McDevitt-Potter et al. (26), a mixed cohort of 70 stable transplant patients converted to generic tacrolimus, including 37 kidney recipients, were examined. Patients in whom stable trough tacrolimus levels had been achieved on an unchanged dose of innovator drug during the previous four wk, and in whom the target level remained constant and no medications known to interact with tacrolimus were started or stopped, were switched to generic tacrolimus on a mg:mg basis. The average time from transplant was 70 months, and the average time from last change in tacrolimus dose was 20 months. The mean tacrolimus trough level was $5.8 \pm 2.1 \text{ ng/mL}$ prior to switch and $5.9 \pm 2.7 \text{ ng/mL}$ after the switch ($p = 0.81$). The mean tacrolimus dose was $4.4 \pm 3.2 \text{ mg/d}$ prior to the switch and $4.5 \pm 2.9 \text{ mg/d}$ afterward ($p = 0.89$). Of the 70 patients switched to generic tacrolimus, 79% required no dose adjustment, 10% required an upward titration, and 11% a downward titration. There were no cases of acute rejection, and only four new AEs were reported (nausea, mouth sores, rash, and vision changes). The authors concluded that dose requirements and trough concentrations were similar between innovator and generic tacrolimus but that additional drug monitoring post-conversion should be recommended as one of every three to four patients may require dose titration.

Momper et al. (27) reported a retrospective, non-randomized, analysis of innovator to generic tacrolimus substitution in 103 stable transplant recipients, including 55 kidney recipients. Transplant recipients had been stable for at least three months post-transplant. In the kidney group, the mean post-transplant time was 48 months and the mean observation period prior to conversion was 47 d and post-conversion 50 d. Target whole blood tacrolimus levels in the kidney recipients were 9–10 ng/mL for the first three months post-transplant and 5–7 ng/mL thereafter. The mean weight adjusted daily dose did not significantly change after conversion (0.087 vs. 0.091 mg/kg/d, $p > 0.05$), but the mean tacrolimus concentration/dose was significantly reduced after conversion (125.3 vs. 110.4 (ng/mL)/(mg/kg/d), $p < 0.05$). Actual trough concentrations declined by an average of 1.98 ng/mL in liver and 0.87 ng/mL in kidney transplant patients following the switch, after accounting for all significant covariates. No appreciable change was observed in biochemical indices of liver function or kidney function following substitution, and there were no cases of acute rejection. Despite the drop in tacrolimus concentrations, the study investigators concluded that the conversion to generic tacrolimus appeared to be
safe when coupled with vigilant therapeutic drug monitoring.

The same study center later reported on a larger cohort, which included 180 kidney recipients (28). These patients were followed for a mean of 104 d prior to and for 422 d after conversion from innovator to generic tacrolimus. There was no statistically significant change to the concentration to dose ratio (ng/mL)/(mg/d) after conversion. Liver function values remained stable but the mean serum creatinine increased from 1.5 to 1.8 mg/dL (p = 0.0002). Acute rejection occurred in 12/180 (6.7%) patients after conversion, although 46 rejection episodes were experienced by this cohort prior to therapy with generic tacrolimus.

Betmouni et al. (29) reported the conversion of 100 stable kidney and pancreas transplant recipients from innovator drug to generic tacrolimus in a UK single-center study. The initial indicator for conversion was cost efficiency, and the cohort was considered as a single group for safety assessments after conversion. After exclusion of eight patients (four received interacting medicines, three reconverted to innovator drug, and one was non-compliant), 92 patients were included for analysis. Mean tacrolimus dose, $C_0$, and serum creatinine remained stable throughout the study. AEs included one case each of rash, headache, and flu-like symptoms, and these were the three patients reconverted back to innovator drug. The authors did not report any cases of acute rejection.

A further retrospective UK single-center study by Shui et al. (30) reported on planned conversion from innovator tacrolimus to generic tacrolimus in 100 stable kidney transplant recipients who were an average of 4.8 yr (range 0.7–23 yr) post-transplant. Ninety-eight patients switched tacrolimus brand, two patients did not consent, and two patients subsequently switched back within two wk due to new symptoms. Post-switch, there was no significant change in mean daily dose (4.7 mg/d pre and 4.8 mg/d post) or $C_0$ level (6.3 ng/mL pre and 6.2 ng/mL post). There were no episodes of rejection, and renal function remained stable. Four patients developed symptoms of dizziness, and seven patients had an increase in blood pressure requiring further treatment.

Spence et al. (31) reported a retrospective analysis of the conversion of 234 clinically stable kidney, liver, and heart transplant recipients to generic tacrolimus six months after transplantation. The 193 kidney transplant recipients had a mean tacrolimus trough concentration (±SD) of 6.79 ± 1.62 ng/mL before conversion and a mean trough concentration (±SD) of 6.97 ± 2.37 ng/mL after conversion, equating to a difference of 0.17 ± 2.33 ng/mL (p = 0.299). Mean follow-up was 106 ± 25 d for all 234 patients. Serum creatinine concentration was 1.33 ± 0.48 mg/dL before conversion and 1.36 ± 0.82 mg/dL after conversion; a difference of 0.04 ± 0.53 mg/dL (p = 0.302). There were no cases of biopsy-proven acute rejection and no deaths. Of 234 (1%), three patients reported new AEs: headache and dizziness, abnormal dreams, and mental slowing. These three patients were also included in the six (of 234) patients who reconverted back to innovator drug.

Rosenborg et al. (32) conducted a prospective study to investigate conversion from innovator tacrolimus to generic tacrolimus in 42 stable kidney transplant patients. The mean ratio of trough concentrations of tacrolimus after compared to before conversion was 1.0 (90% confidence interval, 0.93–1.07). A change of >10% in estimated glomerular filtration rate occurred in eight patients. Changes >20% were not reported in any patient.

Jogia et al. (33) have reported outcomes in 106 stable kidney transplant patients converted to generic tacrolimus from innovator drug. The mean tacrolimus dose was 4.3 ± 2.6 mg/d and 4.1 ± 2.5 mg/d (p = 0.001) pre- and post-conversion, respectively. The mean trough levels at six months pre- and post-conversion were 6.6 ± 1.9 ng/mL and 6.8 ± 1.6 ng/mL (0.161), respectively. No episodes of rejection related to the switch were observed.

Liver

The aforementioned Momper study (27) included 48 liver transplant patients with stable graft function who were at least six months post-transplant. The tacrolimus target concentration in this group was 10–12 ng/mL for the first three months post-transplant, 8–10 ng/mL for months 4–6, and 6–8 ng/mL thereafter. Mean follow-up time pre- and post-conversion was 49 and 58 d, respectively. The mean weight adjusted daily dose did not change significantly (0.039 vs. 0.041 mg/kg/d, p > 0.05), but the mean tacrolimus concentration/dose was significantly reduced after conversion (184.1 vs. 154.7 (ng/mL)/(mg/kg/d), p < 0.05). Renal function and liver function values remained stable, and there were no reported episodes of acute rejection.

A larger cohort involving 203 liver recipients was later reported by the same center (28). This subgroup was followed for a mean of 213 d prior to and for 424 d after conversion. The concentration to dose ratio (ng/mL)/(mg/d) did not significantly change after conversion. Renal function and
liver function values remained stable. There were no acute rejection episodes after conversion, although 66 cases occurred prior to therapy with generic tacrolimus.

In the study by Spence et al. (31), 29 stable liver transplant recipients who had been converted to generic tacrolimus six months after transplantation had trough tacrolimus concentrations of 6.50 ± 1.53 ng/mL before conversion and 6.98 ± 2.14 ng/mL after conversion (p = 0.279). One liver transplant recipient experienced headache and dizziness and switched back to innovator drug. There were no cases of biopsy-proven acute rejection and no deaths.

Other organs

Betmouni et al. (29) reported the conversion of 100 stable kidney and pancreas transplant patients from innovator drug to generic tacrolimus. Although the number of pancreas-alone patients was not stated, it would seem that the conversion was uncomplicated.

The study by McDevitt-Potter et al. (26) included five mixed organ stable transplant recipients, including combined liver-kidney, pancreas after kidney, and kidney-pancreas-liver transplants. The results were not provided separately for these subgroups.

In the Spence study (31), 12 patients with stable heart transplants who were converted to generic tacrolimus six months post-transplant had trough tacrolimus concentrations of 6.36 ± 1.73 ng/mL and 6.73 ± 1.64 ng/mL before and after conversion to generic tacrolimus, respectively (p = 0.215).

Dhungel et al. (34) have performed a retrospective analysis of 21 consecutive patients who were treated with generic tacrolimus following heart transplant and compared rate of biopsy-proven acute cellular rejection to historical controls who were treated with innovator drug. No significant difference in biopsy-proven acute cellular rejection was noted between the groups, and rates of opportunistic infection and death were comparable. Although limited by the single-center, retrospective design, these preliminary data may be useful to clinicians facing the option of initiating generic tacrolimus following heart transplant.

**Dose changes and variability after conversion**

In the cohort of 92 stable kidney and pancreas patients converted from innovator drug to generic tacrolimus, Betmouni and colleagues reported that 14 patients (15%) had an increase in tacrolimus level >2 ng/mL and 11 (12%) had a decrease of <2 ng/mL. Thus, 73% patients maintained stable tacrolimus trough levels within 2 ng/mL of the pre-conversion value (29). Of the 25 (27%) patients with a change in excess of 2 ng/mL, nine (10%) developed levels outside the target range of 5–8 ng/mL.

This experience was mirrored by Shui et al. (30), who found that 15% of patients had a >40% change in level post-switch, although dose changes required to achieve pre-switch levels were small with most patients only requiring a 1–2 mg/d dose change.

In the McDevitt-Potter study (26), dose titrations occurred in five patients (7%) in the control arm and 15 patients (21%) in the study arm (p = 0.028). Fig. 2 shows the number of patients per absolute change in dose and change in tacrolimus trough levels.

In the Momper study (27), there was marked variability between kidney and liver transplant patients in the weight-adjusted tacrolimus dose before and after conversion to generic tacrolimus. However, the mean weight-adjusted daily tacrolimus doses administered to maintain therapeutic trough concentrations were not significantly different between the innovator drug and generic tacrolimus groups in the liver transplant cohort (0.039 vs.
0.041 mg/kg/d, p > 0.05) or the kidney transplant cohort (0.087 vs. 0.091 mg/kg/d, p > 0.05). A total of 43 (42%) patients experienced a dose adjustment after the substitution, with 51.2% of these patients having an increase in tacrolimus dose and 48.8% experiencing a dose reduction.

In the Spence study (31), the mean ± SD daily tacrolimus dose was 4.98 ± 3.37 mg for the innovator drug and 4.99 ± 3.51 mg for generic tacrolimus (p = 0.877). Dosage titrations occurred in 36/234 (15.4%) patients, with 18 titrations downward and 18 upward.

**Conversion protocol and individualizing dose requirements**

There is published experience describing various conversion protocols of innovator drug to generic formulations in stable kidney and liver transplant patients maintained on innovator drug with substitution to generic tacrolimus (16, 20, 26, 27, 29–31, 35).

**Cost effectiveness**

A number of reports have investigated the costs of using generic tacrolimus vs. innovator drug. McDevitt-Potter et al. (26) and Momper et al. (27) discussed various cost savings achieved by switching to generic tacrolimus from innovator drug in liver and kidney transplant recipients. The mean monthly drug costs per patient were found to be US$645 for innovator drug vs. US$593 for generic tacrolimus (~8%) (26). Drug acquisition costs for generic tacrolimus were also found to be 26% less than innovator drug (27). When assessing the costs of therapy in kidney and pancreas patients on a per annum basis, one UK study reported equivalent savings of US$136 000 per 100 patients per year (29). In addition, Spence et al. (31) reported savings in drug acquisition costs of US$45 per patient per month. In all centers, the perceived cost savings need to be balanced with necessary therapeutic drug monitoring, and the additional health care resources needed to safely and effectively transition patients to generic immunosuppressants. It should be noted that cost savings will be country dependent.

**Discussion**

Tacrolimus is a calcineurin inhibitor and is a cornerstone in most immunosuppressive regimens today. Pharmacological bioequivalence has been demonstrated for the immediate release, twice daily formulation of generic tacrolimus (Sandoz), with 90% confidence intervals for the relevant parameters falling within the 90–110% range that is required by the EMA for critical dose drugs. Both de novo and conversion clinical experience with generic tacrolimus have been reported in renal, liver, and other SOT patients.

Current opinion among the transplant community is that the use of generic immunosuppressive therapy in preference to branded drugs is safe, but that certain precautions are needed (36). It is imperative that clinicians are aware of the lack of proven bioequivalence between different generic compounds, and that stringent therapeutic drug monitoring is in place during the initial switch phase (15). In addition, the increasing prevalence of generic immunosuppression dictates that patient education and information are paramount in order to avoid medication errors arising as a result of a lack of clarity regarding an individual patient’s medications and to ensure adherence to therapy (17, 36).

The narrow therapeutic index of tacrolimus and the severity of the potential adverse consequences of subtherapeutic and toxic concentrations necessitate close monitoring of patients’ exposure to the drug. Units introducing the generic formulations of tacrolimus must therefore implement measures to prevent the inadvertent or unsupervised substitution of different formulations, particularly given that immediate- or prolonged-release tacrolimus formulations are both available. Aside from deliberate conversions, patients should be maintained on a single formulation of tacrolimus (9).

Guidance intended to reduce the risk of medication errors with tacrolimus advocates that prescribers use either the exact and full pharmaceutical form (capsules or granules; intermediate or prolonged release) or the brand name, including the dose and frequency in both cases (37). Patients should be advised to note the brand name of their tacrolimus medicine (37).

**Summary**

The use of generic immunosuppression is increasing. This article has reviewed the existing literature regarding the use of generic tacrolimus in transplantation, illustrating that its use is increasingly widely considered to be safe, efficacious, and cost effective in both de novo and stable transplant patient groups, but that conversion programs require increased therapeutic drug monitoring.

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