The Skinny on Narrow Therapeutic Index Drugs Used in Transplantation: A Brand vs. Generic Debate

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Learning Objectives:
1. Describe characteristics of narrow therapeutic index (NTI) drugs
2. Identify immunosuppressants which meet NTI criteria
3. Discuss the FDA approval process for innovator and generic drug products
4. Compare the conflicting bioequivalence and clinical literature regarding switchability of immunosuppressant medications
5. Devise an evidence-based approach for use of differing formulations of NTI immunosuppressants in the solid organ transplant population
BACKGROUND

I. “Narrow Therapeutic Index” (NTI) Drugs
   A. United States Food and Drug Administration (FDA)\textsuperscript{1,2}
      i. Definition of drug with narrow therapeutic range: “Drug substances subject to therapeutic
drug concentration or pharmacodynamic monitoring, and/or where product labeling
indicates a narrow therapeutic range designation”\textsuperscript{2}
      ii. According to Federal Register [21 CFR 320.33(c)], FDA defines a drug as having a
narrow therapeutic range if:
         a. Less than 2-fold difference between median lethal and median effective dose, or
         b. Less than 2-fold difference between minimum toxic and minimum effective
concentrations in the blood, and
         c. Safe and effective use of the drug product requires careful titration and patient
monitoring

II. NTI Law
   A. FDA/Center of Drug Evaluation and Research (CDER)\textsuperscript{3,4}
      i. FDA has not developed a formal list of NTI drugs
      ii. CDER developed a sample list of NTI drugs in 1988, including digoxin, theophylline,
carbamazepine, and warfarin, among others
   B. North Carolina
      i. North Carolina Board of Pharmacy establishes a list of NTI drugs annually
   C. Texas\textsuperscript{6}
      i. Texas State Board of Pharmacy (TSBP) was given authority to create a list of NTI drugs,
but to date no drugs added
      ii. In 2007, amendments were proposed to include Prograf\textsuperscript{®}, Cellcept\textsuperscript{®}, Neoral\textsuperscript{®},
Rapamune\textsuperscript{®}, and Sandimmune\textsuperscript{®} on an NTI list which would result in dispensing
restrictions similar to North Carolina
         a. A joint committee consisting of members of the TSBP and Texas Medical Board
recommended that no drugs be added to the NTI list
         b. A similar committee met in 2008 to consider adding anti-epileptic drugs which also
resulted in no additions to the NTI list

<table>
<thead>
<tr>
<th>Table 1: List of North Carolina NTI drugs\textsuperscript{5}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Cyclosporine (Sandimmune\textsuperscript{®} and Neoral\textsuperscript{®})</td>
</tr>
<tr>
<td>Digoxin</td>
</tr>
<tr>
<td>Ethosuximide</td>
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<tr>
<td>Levothyroxine</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
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</table>

ii. Drugs identified as NTI are required to be refilled using only same drug product by same
manufacturer last dispensed unless prescriber is notified by the pharmacist prior to
dispensing and, the prescriber and patient give documented consent
III. FDA Approval
   A. Innovator compounds\textsuperscript{7,8}
      i. Extensive testing from pre-clinical development \(\rightarrow\) Phase III
      ii. Laboratory and animal studies \(\rightarrow\) healthy volunteers \(\rightarrow\) targeted patients
      iii. New Drug Application (NDA)
   B. Generic compounds\textsuperscript{8,9}
      i. Generics not required to submit safety and clinical data of active ingredients (previously provided by innovator product)
      ii. Only bioequivalence testing required
      iii. Abbreviated New Drug Application (ANDA)
   C. Bioequivalence\textsuperscript{8}
      i. Absence of a significant difference in rate and extent to which the active ingredient becomes available at the site of drug action
      ii. Generic contains the same active ingredient at the same strength, dosage form and route of administration
      iii. Allowed to differ in shape, release mechanisms, excipients, packaging, expiration time, and, within certain limits, labeling
      iv. Typical study
         a. Single-dose, two-way crossover design comparing blood concentrations of the reference and generic product over time in 24-36 healthy subjects
         b. Maximum concentration (\(C_{\text{max}}\)) and area under the curve (AUC) determined
            1. Must have 90\% confidence that they fall within 80-125\% of innovator product

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{bioequivalence.png}
\caption{Schematic diagram illustrating possible bioequivalence study outcomes. T/R = test/reference\textsuperscript{10}}
\end{figure}

IV. Solid Organ Transplant
   A. Treatment of choice for many end stage organ diseases
   B. Success of transplantation has increased organ demand and led to a critical imbalance between demand and supply
C. More than 105,000 people in the US are currently waiting for an organ transplant\textsuperscript{11}  
   i. 21,423 transplants have been performed from January-September 2009  
   ii. Nearly 4,000 candidates are added to the waiting list each month  
   iii. Over 7,000 candidates die yearly waiting for transplant

V. Immunosuppressant Use for Maintenance Therapy in Transplant Patients\textsuperscript{12,13}  
A. Overview  
   i. Immunosuppressants are mainstay of post-transplant therapy  
   ii. Goal of maintenance immunosuppression: prevent graft rejection, minimize adverse drug effects, and avoid infectious complications  
   iii. Multi-drug approach: utilizing agents with multiple mechanisms of action permits use of lower doses of single agents; minimizing severity of adverse drug effects  
   iv. Choice of immunosuppression regimen is multi-factorial:  
      a. Institution protocol  
      b. Transplanted organ type  
      c. Individual donor and recipient risk factors  
      d. Financial considerations  
      e. Patient adherence  
B. Classification of drug categories  
   i. Corticosteroids (CS)  
   ii. Calcineurin inhibitors  
      a. Cyclosporine (CsA; Neoral\textsuperscript{®}, Sandimmune\textsuperscript{®})  
         1. Sandimmune\textsuperscript{®} = cyclosporine – an oil based formulation with significant interpatient and intrapatient variability due to bile-dependent absorption of cyclosporine  
         2. Neoral\textsuperscript{®} = (cyclosporine capsules, USP) MODIFIED and (cyclosporine oral solution, USP) MODIFIED – a microemulsion designed to reduce variability in absorption of cyclosporine  
         3. Neoral\textsuperscript{®} and Sandimmune\textsuperscript{®} formulations are not interchangeable  
      b. Tacrolimus (TAC; Prograf\textsuperscript{®})  
   iii. Antiproliferative agents  
      a. Azathioprine (AZA; Imuran\textsuperscript{®})  
      b. Mycophenolate (MMF/MPS; CellCept\textsuperscript{®}, myfortic\textsuperscript{®})  
         1. CellCept\textsuperscript{®} = mycophenolate mofetil  
         2. myfortic\textsuperscript{®} = enteric coated mycophenolate sodium  
         3. CellCept\textsuperscript{®} and myfortic\textsuperscript{®} formulations are not interchangeable  
   iv. Target-of-rapamycin (mTOR) inhibitors  
      a. Sirolimus (SIR; Rapamune\textsuperscript{®})  
      b. Everolimus (Certican\textsuperscript{®}) – Not approved in the US  

VI. NTIs in Transplant\textsuperscript{5,14,15}  
A. Tacrolimus  
   i. Significant correlation between tacrolimus trough levels (C\textsubscript{0}) and both rejection and toxicity\textsuperscript{14,17}
B. Cyclosporine
   i. $C_0$ levels monitored with Sandimmune® and Neoral® to minimize drug toxicity and maximize clinical efficacy\textsuperscript{15}
   ii. Cyclosporine modified (Neoral®)\textsuperscript{16}
      a. Significant correlation between 2-hour post-dose cyclosporine ($C_2$) level <1500 ng/mL and acute rejection frequency within 7 days post transplant
      b. Association with elevated $C_2$ levels and worsening renal function and more frequent/more severe hypertension
   iii. The Consensus on Neoral® $C_2$: Expert Review in Transplantation (CONCERT)\textsuperscript{16}
      a. $C_2$ levels are the preferred monitoring method compared with $C_0$ in de novo renal and liver transplant recipients
      b. $C_2$ monitoring may be beneficial in maintenance renal and liver transplant recipients
C. Sirolimus
   i. Significant correlation between sirolimus $C_0$ concentrations <5 ng/mL and frequency/severity of acute rejection
   ii. Significant correlation between sirolimus $C_0$ concentrations >15 ng/mL and occurrence of toxicity (thrombocytopenia, leukopenia, and hypertriglyceridemia)\textsuperscript{14,18}
D. Mycophenolate
   i. Utility of therapeutic drug monitoring of mycophenolic acid highly debated\textsuperscript{15,19}
   ii. Status of mycophenolate sodium and mycophenolate mofetil as NTI drugs is also questioned as both are absent from approved narrow therapeutic index drug lists\textsuperscript{5,14}

<table>
<thead>
<tr>
<th>Calcineurin Inhibitors</th>
<th>Sirolimus</th>
</tr>
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<tbody>
<tr>
<td>Hypertension</td>
<td>Leukopenia</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Hypertriglyceridemia</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>Pneumonitis</td>
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<td></td>
<td>Aphthous Ulcers</td>
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</tbody>
</table>
Table 3: NTI Immunosuppressant Brand vs. Generic Timeline\textsuperscript{22-24}

<table>
<thead>
<tr>
<th>Date</th>
<th>Significant Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>November 1983</td>
<td>Sandimmune\textsuperscript{®} (cyclosporine) oral solution approval</td>
</tr>
<tr>
<td>July 1992</td>
<td>Current bioequivalence criteria (AUC and C\textsubscript{max} range of 80% to 125% based on two one-sided tests)</td>
</tr>
<tr>
<td>March 1990</td>
<td>Sandimmune\textsuperscript{®} (cyclosporine) capsule approval</td>
</tr>
<tr>
<td>April 1994</td>
<td>Prograf\textsuperscript{®} (brand tacrolimus) capsules approval</td>
</tr>
<tr>
<td>July 1995</td>
<td>Neoral\textsuperscript{®} capsules and solution approval (brand cyclosporine modified)</td>
</tr>
<tr>
<td>October 1998</td>
<td>SangStat’s SangCya\textsuperscript{®} (generic cyclosporine modified) approval</td>
</tr>
<tr>
<td>September 1999</td>
<td>Rapamune\textsuperscript{®} (sirolimus) solution approval</td>
</tr>
<tr>
<td>January 2000</td>
<td>Cyclosporine modified capsules (Sandoz) approval</td>
</tr>
<tr>
<td>May 2000</td>
<td>Cyclosporine modified capsules (Gengraf\textsuperscript{®}, Abbott)</td>
</tr>
<tr>
<td>August 2000</td>
<td>Rapamune\textsuperscript{®} (sirolimus) tablet approval</td>
</tr>
<tr>
<td>December 2000</td>
<td>SangCya\textsuperscript{®} withdrawal</td>
</tr>
<tr>
<td>December 2000</td>
<td>Cyclosporine modified capsules (Pliva) approval</td>
</tr>
<tr>
<td>December 2001</td>
<td>Cyclosporine modified solution (Pliva) approval</td>
</tr>
<tr>
<td>May 2002</td>
<td>Cyclosporine capsules (generic Sandimmune\textsuperscript{®}, Apotex) approval</td>
</tr>
<tr>
<td>September 2004</td>
<td>Cyclosporine solution (generic Sandimmune\textsuperscript{®}, Morton Grove) approval</td>
</tr>
<tr>
<td>January 2005</td>
<td>Cyclosporine modified solution (Novex) approval</td>
</tr>
<tr>
<td>March 2005</td>
<td>Cyclosporine modified capsules and solution (Ivax) approval</td>
</tr>
<tr>
<td>August 10, 2009</td>
<td>Tacrolimus (Sandoz) capsules approval</td>
</tr>
<tr>
<td>2010</td>
<td>Extended release tacrolimus?</td>
</tr>
<tr>
<td>2010</td>
<td>Sirolimus generic? Exclusivity expiration January 2010</td>
</tr>
</tbody>
</table>
THE DEBATE

- Are bioequivalence studies adequate for NTI immunosuppressants?
- What is the cost difference?
- Are generic and brand NTI immunosuppressants equally effective?

Are Bioequivalence Studies Adequate For Generic Immunosuppressants?

**GENERIC**

I. United States FDA Position
   A. Drug Price Competition and Patent Term Restoration Act 1984 (Waxman-Hatch Amendments)\textsuperscript{25}
      i. Established abbreviated new drug application (ANDA) process
      ii. Authorized extension of patent term of new drugs
      iii. Reasons for amendments
          a. Promote market competition
          b. Encourage scientific research
          c. Decrease time from generic drug application to approval
          d. Increase availability of therapeutically equivalent products, reducing health care expenditures
          e. Prevent duplicate animal studies and clinical trials in humans
          f. Provide market exclusivity and patent term restoration to secure interest in drug development
   B. Actual brand/generic variance\textsuperscript{10}
      i. Generic drugs approved by the FDA from 1996 to 2007
         a. Average difference of $C_{\text{max}}$ and AUC between generic and brand was 4.35% and 3.56%, respectively
         b. In 98% of bioequivalence studies, the difference between brand and generic varied less than 10%; of those drugs which varied $\geq$ 10%:
            1. None were immunosuppressant drugs
            2. None were considered narrow therapeutic index drugs
            3. Most were drugs with intra-patient variability $\geq$ 30% in $C_{\text{max}}$ and AUC
            4. Highly variable drugs seldom meet FDA bioequivalence criteria
            5. No excipients were identified to contribute to bioavailability differences
   C. FDA supports substitution of all generic products for innovator drugs\textsuperscript{1,10}
      i. Confirms that rate and absorption vary minimally between all approved generic versus brand products
         a. Any difference in plasma concentration would have a clinically insignificant effect\textsuperscript{10}
         b. Typically, other factors can cause changes in drug plasma concentrations which exceed any minor change that would be a consequence of generic substitution\textsuperscript{10,25}
            1. Addition, discontinuation, or dose change in interacting drug therapy
            2. Variance in patient drug therapy adherence
      ii. Assures approval process validated as ANDA applicants must submit the same drug substance and product CMC (Chemistry, Manufacturing, and Controls) data as NDA applicants\textsuperscript{10}
   D. NTI immunosuppressants need not be treated any different than all other drugs\textsuperscript{1}
i. Current evidence is insufficient that use of single patient population bioequivalence studies would demonstrate clinically significant results\(^1\)
   a. Transplant patients represent a heterogeneous population\(^27\)
      1. Subpopulations of poor drug absorbers
      2. Large degree of pharmacokinetic variability
   b. For bioequivalence studies to reach significant statistical power with a transplant patient group, a much larger sample size would be required than with healthy individuals\(^28\)
      1. Recruitment may be limited

ii. Multiple-dose studies are unnecessary as single-dose bioequivalence studies are more sensitive at identifying differences in product formulations\(^2,28\)
   a. Single-dose studies preferred by FDA for generic approvals\(^2\)
   b. With specific patient transplant populations, multiple-dose studies are typically required due to ethical concerns with single dose studies\(^1\)

II. Variability with NTI Immunosuppressants

A. Tacrolimus
   i. Tacrolimus mean intrasubject variability has been reported as 12.7\%-23.4\% when accounting for AUC and C\(_{\text{max}}\) in healthy individuals given two single doses of tacrolimus spaced 7 days apart\(^29\)

B. Cyclosporine
   i. Cyclosporine modified intrasubject variability = 13.1\% for C\(_{\text{max}}\) and 8.8\% for AUC\(^30\)
   ii. Cyclosporine (Sandimmune\(^\text{®}\)) intrasubject variability = 23\% for C\(_{\text{max}}\) and 19.3\% for AUC\(^31\)
   iii. In stable renal transplant patients maintained on controlled doses of cyclosporine, variability of cyclosporine concentrations was 26\% for C\(_0\) and 19\% for C\(_2\) between two outpatient transplant clinic visits\(^31\)

C. Sirolimus
   i. Dose-adjusted intrapatient variability of sirolimus C\(_0\) levels within renal transplant patients was 42.8\%±16.2\%\(^32\)
   ii. During clinical trials, intrapatient variability of sirolimus C\(_0\) levels was approximately 35\%\(^33\)

D. Factors affecting NTI drug concentration\(^34\)
   i. Drug-drug interactions – alteration of efflux pump and enzyme activity by concomitant medications
   ii. Genetic polymorphisms
   iii. Age
   iv. Drug-food interactions
   v. Disease

III. Change in Innovator Product Formulation\(^35\)

A. 62\% of new chemical entities approved as oral agents from 1981 to 1990 were marketed as different formulations than those used in phase III trials
   i. Marketed products were approved based on single-dose data in healthy individuals comparing them to formulations utilized in phase III trials

B. FDA approved new formulations of innovator Neoral\(^\text{®}\), Sandimmune\(^\text{®}\), and Prograf\(^\text{®}\) based exclusively on bioequivalence studies
IV. Supporting Bioequivalence Literature Within Transplant Patients

A. Roza et al.36


**Design**
- Five week, open-label, three-period design, multicenter conversion trial

**Location**
- WI, CA, MI, IL, TX, SC, VA, & CA, USA

**Generic Utilized**
- Gengraf® by Abbott Laboratories (CsA microemulsion approved in US)

**Study Methods**
- N=50 renal transplant patients, ≥ 6 months post-transplant, on stable dose Neoral® with stable C0 for ≥ 2 months
- Conversion of patients from Neoral® to Gengraf®: days 1-14 = baseline Neoral® dose (twice daily), days 15-28 = converted to Gengraf® on dose-for-dose basis, & days 29-35 = converted back to Neoral® on dose-for-dose basis
- Medications known to significantly interact with CsA pharmacokinetics were not permitted

**Objectives**
- **Primary:** to evaluate the interchangeability of Neoral® and Gengraf® by analyzing CsA Cmax, AUC0→12hr, Cmin and Tmax on days 1 and 14 (Neoral®), days 15 and 28 (Gengraf®), and day 29 (Neoral®)
- **Secondary:** evaluate safety and tolerability of switching from Neoral® to Gengraf®

**Results**
- No statistically significant differences in Cmax, AUC0→12hr, Cmin and Tmax between Neoral® at day 14 and Gengraf® at day 28
- Bioequivalence of Neoral® and Gengraf® in stable renal transplant recipients (all 90% CI within 0.8-1.25)

<table>
<thead>
<tr>
<th>Study Days</th>
<th>PK Variable</th>
<th>Ratio (Test/Reference)</th>
<th>90% CI</th>
</tr>
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<tbody>
<tr>
<td>Gengraf® vs Neoral® at steady state 28 vs. 14</td>
<td>Cmax after 2 weeks of CsA</td>
<td>0.981</td>
<td>0.922-1.044</td>
</tr>
<tr>
<td></td>
<td>AUC after 2 weeks</td>
<td>0.992</td>
<td>0.951-1.034</td>
</tr>
<tr>
<td>Switchability of Neoral® to Gengraf® 15 vs. 14</td>
<td>Cmax after 1 day</td>
<td>0.908</td>
<td>0.848-0.973</td>
</tr>
<tr>
<td></td>
<td>AUC after 1 day</td>
<td>0.956</td>
<td>0.923-0.990</td>
</tr>
<tr>
<td>Switchability of Gengraf® to Neoral® 28 vs. 29</td>
<td>Cmax after 1 day</td>
<td>1.012</td>
<td>0.950-1.077</td>
</tr>
<tr>
<td></td>
<td>AUC after 1 day</td>
<td>0.999</td>
<td>0.951-1.047</td>
</tr>
</tbody>
</table>

- Adverse events: one serious adverse event (pyelonephritis) reported on day 4 (while on Neoral®)
- No graft rejection occurred
- No cyclosporine dosage adjustments were necessary throughout study period
- Serum creatinine: No significant difference throughout study (day 1, 1.32±0.45 mg/dL; day 4, 1.35±0.46 mg/dL; day 14, 1.31±0.47 mg/dL; day 28, 1.29±0.44 mg/dL; day 29, 1.23±0.42 mg/dL)

**Conclusions**
- Trial demonstrated that kidney transplant recipients, both male and female, could safely convert from Neoral® to Gengraf®, and vice versa, on a dose for dose basis

**Study Strengths**
- Multicenter within U.S.
- Utilized FDA-approved generic
- Results suggest that bioequivalence studies within healthy adults are predictive of bioequivalence in stable renal transplant recipients

**Study Limitations**
- Authors stated that no PK differences existed for gender, but not powered to show statistical differences for subpopulation
BRAND

I. Bioequivalence Studies

A. Study design

i. Acceptable confidence intervals for NTI drugs

a. US: AUC 80-125%\(^2,8\)

1. Although the average drug’s Cmax and AUC differ only ~4% from reference formulation, a significant number of drugs differ by a greater percentage\(^{10}\)

   – 174 generics had a Cmax difference of >10%
   – 8 generics had a Cmax difference >15%
   – 49 generics had AUC differences >10%
   – 2 generics had AUC differences >15%

b. Canada: AUC 90-112% for NTI drugs\(^{38}\)

   1. Includes tacrolimus, cyclosporine, and sirolimus

ii. Generics are deemed bioequivalent to brand, but not necessarily each other

a. Potentially resulting in a difference in AUC or C\(_{\text{max}}\) of >20%


Figure 3: Bioequivalence figures with both Brand and Generic A as the reference formulation

B. Study population

i. Typical bioequivalence study done in 24-36 young, healthy, male volunteers\(^{8}\)

ii. Transplant population is very different

a. Multiple co-morbidities, single and multiple organ failure
b. Goal therapeutic ranges and pharmacokinetics are organ specific

   1. Mean clearance after IV administration of tacrolimus was 0.083 L/hr/kg in adult kidney transplant recipients compared with 0.040 L/hr/kg in healthy volunteers\(^{39}\)

c. On average, transplant patients take 10 different medications simultaneously\(^{30}\)
d. Special populations such as pediatrics and African Americans are not considered\(^{37}\)

   1. Pediatric patients frequently require 2-4 times the dose of tacrolimus to maintain similar C\(_0\) concentrations as adults
   2. African Americans require significantly higher mg/kg doses to achieve similar C\(_0\) concentrations as non-African Americans
C. FDA acknowledges limitations
   i. 2003 FDA Guidance on General Bioavailability/Bioequivalence Issues
      a. FDA recognized the need to “provide increased assurance of the interchangeability for drug products containing NTI drugs”
      b. Guidance merely recommended, however, that sponsors “consider additional testing and/or controls to ensure the quality of drug product containing NTI drugs”

II. Supporting Literature
   A. SangCya® versus Neoral® oral solution
      i. Approved in 1998 after successful bioequivalence studies in healthy volunteers
      ii. Additional studies demonstrated that healthy volunteers who took SangCya® with apple juice absorbed 20% - 30% less those taking Neoral®
      iii. FDA: not bioequivalent
         a. Class II recall and product voluntarily withdrawn from market (2000)
   B. Qazi YA et al.42

<table>
<thead>
<tr>
<th>Design</th>
<th>Randomized, prospective, single center study</th>
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<tbody>
<tr>
<td>Location</td>
<td>Buffalo NY, USA</td>
</tr>
<tr>
<td>Generic Utilized</td>
<td>Gengraf® by Abbott Laboratories</td>
</tr>
<tr>
<td>Methods</td>
<td>Renal transplant patients at least 6 months post-transplant with stable graft function, stable C₀ over past 3 visits, and currently receiving Neoral® twice daily</td>
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<tr>
<td></td>
<td>Randomized to either remain on Neoral® (10%) or to be switched to Gengraf® (90%)</td>
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<tr>
<td></td>
<td>C₀ checked 2 weeks after start of study, and repeated in 4 weeks</td>
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<tr>
<td></td>
<td>Dosages adjustments were made if C₀ levels changed by ≥ 20% from baseline</td>
</tr>
<tr>
<td>Objective</td>
<td>Evaluate effect of 1:1 dose conversion from Neoral® to Gengraf®</td>
</tr>
<tr>
<td>Results</td>
<td>No patients started a new medication or required a dose change in any pre-existing medications that would impact C₀ concentrations</td>
</tr>
<tr>
<td></td>
<td>82 patients enrolled, 73 were switched to Gengraf®</td>
</tr>
<tr>
<td></td>
<td>13/73 required a dosage change at 2 weeks (12/13 for elevated C₀)</td>
</tr>
<tr>
<td></td>
<td>- Baseline C₀ 234 vs 289 ng/mL at week 2 (p &lt;0.05)</td>
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<tr>
<td></td>
<td>- After dosage adjustment C₀ returned to baseline at week 4 (239 ng/mL)</td>
</tr>
<tr>
<td></td>
<td>0/9 patients required dosage change in Neoral® group</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Results raise serious concerns regarding interchangeability of Gengraf® for Neoral® without careful follow-up therapeutic drug monitoring</td>
</tr>
<tr>
<td>Study Strengths</td>
<td>Randomized, prospective design</td>
</tr>
<tr>
<td></td>
<td>Patients on stable doses prior to switch</td>
</tr>
<tr>
<td></td>
<td>No changes in interacting medications could affect results</td>
</tr>
<tr>
<td>Study Limitations</td>
<td>Small number of patients remained on Neoral®</td>
</tr>
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III. Expert Opinion
   A. National Kidney Foundation White Paper recommendations
      i. Include cyclosporine and tacrolimus into critical dose drug category
      ii. Use of pharmacokinetic studies with replicate design for establishing bioequivalence
      iii. Generics should demonstrate bioequivalence in target populations
      iv. Emphasize need for physician and patient notification when immunosuppressants are substituted from one formulation to another
      v. Implement appropriate monitoring when immunosuppressants are substituted from one formulation to another
B. American Society of Transplantation recommendations\textsuperscript{44}
   i. Maintain consistent use of selected immunosuppression formulation
   ii. Establish pill and container uniqueness among generics
   iii. Ensure patients are educated so physicians are informed when switch occurs so appropriate follow-up can take place
   iv. Incorporate bioequivalence studies in at-risk patient populations into generic drug approval process
C. American Society of Transplant Surgeons (ASTS)\textsuperscript{37}
   i. “...the currently proposed guidelines for demonstrating bioequivalence for transplant indications are far too loose and could be potentially dangerous.”
   ii. Bioequivalencse studies for generic immunosuppressants must include stable transplant patients at the very least

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**What is the Cost Difference?**

**GENERIC**

I. Cost difference between brand vs. generic products
   A. In 2007, the National Association for Chain Drug Stores reported average prices for:\textsuperscript{45}
      i. Brand name prescription = $119.51
      ii. Generic prescription = $34.34
   B. Brand vs. generic cyclosporine modified
      i. Estimated annual mean cost benefit of switching from Neoral\textsuperscript{®} to generic cyclosporine modified (Gengraf\textsuperscript{®}, Abbott Laboratories) for VA pts = US$892 per patient\textsuperscript{46}
         a. Extrapolated cost savings could be greater than US$2.5 million per year for VA patients nationwide
         b. In September 2001, VA costs for Gengraf\textsuperscript{®} were 21% lower than Neoral\textsuperscript{®}
      ii. As of November 2009, according to University Hospital wholesaler, Morris & Dixon, the package cost of Gengraf\textsuperscript{®} was approximately 14% lower than Neoral, while the outpatient pharmacy contract price of Gengraf\textsuperscript{®} was 36% lower than Neoral\textsuperscript{47}
   C. Brand vs. generic Tacrolimus
      i. University Hospital outpatient cost for tacrolimus by Sandoz ranged from 2-8% lower than Prograf\textsuperscript{®}\textsuperscript{49}

II. Effects on Patient Compliance
   A. Association with graft failure and inability to afford immunosuppressants\textsuperscript{48}
      i. Estimated range of graft failures due to medication nonadherence = 11-52%
      ii. Medication nonadherence is more common in unemployed patients and patients of lower socioeconomic status
   B. Statement by the American Society of Transplantation\textsuperscript{34}

Participants strongly support the availability of efficacious, less expensive, immunosuppressive medications and endorse efforts to introduce generic alternatives...
Medication costs may contribute to noncompliance with prescribed medical regimens...
III. Generic Carve-Out Legislation\(^4^9\)

A. Proposed legislation would require pharmacists to obtain physician permission before substituting a generic equivalent for specific brand name drugs, including immunosuppressants, antipsychotic agents, and antiepileptics

B. Analysis conducted by Visante, Inc., estimated the 10-year economic impact of potential nationwide generic carve-out legislation

   i. Only included immunosuppressants anticipated to have generic alternatives introduced between 2009 and 2019 (myfortic\(^\text{®}\), CellCept\(^\text{®}\), Prograf\(^\text{®}\), and Rapamune\(^\text{®}\))

      a. Excluded cyclosporine modified from analysis

   ii. Results

| Table 4: Estimated 10-Year Impact of Generic Carve-Out Legislation Applied to Immunosuppressants |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Total                          | Medicaid (State) | Medicaid (Federal) | Third Party Payors and Medicare | Consumer Out-of-Pocket |
| US Total                      | $4,094          | $185              | $242                          | $2,995                          | $672                          |
| Texas Total                   | $324.5          | $11.6             | $17.8                         | $245.4                          | $49.7                          |

(Dollar Figures in Millions)

iii. Strengths

   a. Accounted for effects of manufacturer rebates, product line extension (namely extended release tacrolimus), and possible new chemical entity approvals

iv. Weaknesses

   a. Assumed all generic product prices would average 40% of brand name products price

   b. Anticipated that percent of prescriptions dispensed would decrease from 90% generic to 25% generic for specified drug\(^4^9,5^0\)

   c. Conclusions derived from data not specific to drugs classified as NTI

**BRAND**

I. Acquisition Cost

A. Brand generally more expensive

B. Patient assistance programs can counter costs

   i. Astellas Patient Assistance Program for Organ Transplant (Prograf\(^\text{®}\))

   ii. Novartis Patient Assistance Program (Neoral\(^\text{®}\))

   iii. RapAssist\(^\text{®}\) Patient Assistance Program (Rapamune\(^\text{®}\))

II. Other Important Costs to Consider

A. Supratherapeutic levels\(^5,1^2,1^5\)

   i. Dosage adjustments, more frequent clinic visits to monitor concentrations

   ii. Significant adverse effects

      a. Patient may experience increased side effects suggesting elevated levels

      b. Nephrotoxicity, neurotoxicity, electrolyte abnormalities, infections, hematologic side effects

      c. Ultimately may lead to increased hospitalizations, graft loss, and death

B. Subtherapeutic levels\(^1^4,1^8\)

   i. Asymptomatic

   ii. Acute rejection

      a. Increased frequency of clinic visits, hospitalizations
b. Treatment of rejection\textsuperscript{51}
   1. Estimated costs of approximately $3,300 for a treatment course of corticosteroids
      and $14,500-$18,000 for a course of antilymphocyte therapy

iii. Graft failure
   a. Hospitalizations, relisting if eligible for transplant, death
   b. Maintenance costs until organ becomes available
   c. Example: renal graft failure\textsuperscript{52}
      1. Medicare’s cost of maintaining a kidney transplant recipient for the first year
         post-transplant is approximately $13,000 vs $135,000 for the year following
         graft failure and return to dialysis
      2. Patients with graft failure are much more likely to miss work and remain on
         disability
      3. Patient’s quality of life is drastically worsened

iv. Re-transplant\textsuperscript{53}
   a. In 2008, average first year billed charges per kidney transplant was $259,000
      1. Immunosuppressants accounted for only 6.6\% of total charge
   b. The average charges for liver and heart transplants were significantly higher at
      $523,400 and $787,700, respectively
      1. Immunosuppressants account for only 2.6-4\% of total charge

III. Brand Drug Perks
    A. Patient programs
       i. Astellas’ “Transplant Experience,” Roche’s “CellCept\textsuperscript{®} for Living”
       ii. Educational materials, medication schedules and tools, updates on news and events in
           transplant community, support groups, etc.
    B. Research support
    C. Meeting funding for providers

Are the Generic and Brand Immunosuppressants Equally Effective?

\textbf{GENERIC}

I. American Medical Association Position\textsuperscript{54}
   A. Statement regarding NTI drugs (specifically reviewing cyclosporine literature):

\begin{quote}
While concerns still persist among some physicians about the therapeutic equivalence of generic NTI
drugs to their brand name innovator products, scientific evidence to support these concerns either does
not exist or is extremely weak...Theoretical assumptions of the possibility of inequivalence are not a
sufficient basis for presuming its presence and acting on that assumption.
\end{quote}
II. Supporting literature
A. Carnahan et al.46

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<tbody>
<tr>
<td><strong>Design</strong></td>
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<td><strong>Location</strong></td>
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<tr>
<td><strong>Generic Utilized</strong></td>
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| **Study Methods** | ● Outpatient renal transplant patients converted from Neoral® to equivalent dose of Gengraf® due to formulary changes  
   ● N=41 kidney transplant recipients  
   ● Classified based on CsA steady state C₀ as subtherapeutic, supratherapeutic, or therapeutic  
     - Goal 0-3 months post transplant = 300±25 ng/mL  
     - Goal 3-6 months post transplant = 250-300±25 ng/mL  
     - Goal 6-12 months post transplant = 200-250±25 ng/mL  
     - Goal 12-18 months post transplant = 200±25 ng/mL  
     - Goal >18 months post transplant = 100-150±25 ng/mL |
| **Objectives** | ● Primary: to assess differences in steady state CsA C₀ and serum creatinine from baseline to last laboratory follow-up  
   ● Secondary: to evaluate changes in CsA dosing regimen, CsA toxicity, graft rejection, hospital/emergency room admission, and changes with CsA interacting therapy |
| **Results** | ● Duration: average length from enrollment to last laboratory follow-up: 18 weeks (Range = 3-27 weeks)  
   ● Patients at therapeutic concentration: no significant difference; 63.4% with Neoral® at baseline and 80.5% with Gengraf® at last follow-up (p=0.085)  
   ● Serum creatinine: 1.71 mg/dL at baseline and 1.68 mg/dL at followup (p=0.447)  
   ● No reports of graft rejection, CsA toxicity, or hospitalization due to generic conversion  
   ● Patients with graft age > 18 months (n=29):  
     - Mean CsA C₀ = 156 ng/mL at baseline and 139 ng/mL at follow-up (p=0.078)  
     - 69% were therapeutic at baseline and 79.3% were therapeutic at follow-up (p=0.3725)  
     - Two required CsA dose changes; correlated with change in medication therapy with a drug known to alter CsA metabolism |
| **Conclusions** | Gengraf® and Neoral® are therapeutically equivalent in renal transplant recipients |
| **Study Strengths** | ● Assessed renal transplant patients in a clinical setting utilizing similar methods as other transplant centers would utilize when converting patients from brand to generic CsA  
   ● No reports of clinical failure |
| **Study Limitations** | ● Small sample size  
   ● Short duration of follow-up  
   ● CsA C₀ concentrations measured at several different laboratories  
   ● Standard deviation of CsA C₀ >18months post transplant not reported  
   ● Utilization of C₀ vs C₂ |
**BRAND**

I. Supporting Literature

A. Taber et al.55


<table>
<thead>
<tr>
<th>Design</th>
<th>Retrospective, single center study</th>
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<tbody>
<tr>
<td>Location</td>
<td>South Carolina, USA</td>
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**Study Methods**

- N=188 adult de novo kidney transplant recipients
  - 57% African Americans, 83% cadaveric transplants
  - 100 patients received Gengraf®, 88 patients received Neoral®
- Assessed biopsy proven acute rejection (BPAR)
- All patients received triple drug immunosuppression consisting of cyclosporine, mycophenolate mofetil, and a standard prednisone taper
- Patients on Neoral® were transplanted between January 1999 and May 2001
- Patients on Gengraf® were transplanted between May 2001 and July 2002
- Initial CsA dose was 4-5mg/kg PO BID
- Target 12 hour $C_0$ concentrations were:
  - 350-400 ng/mL weeks 1-4
  - 250-350 ng/mL weeks 5-12
  - 200-300 ng/mL weeks 13-52

**Objectives**

- Primary: to evaluate BPAR at 6 months post-transplant
- Secondary endpoints: to analyze incidence of second BPAR, patient and graft survival, 12-hour $C_0$ cyclosporine concentrations for first 14 days post-transplant, severity of BPAR, and use of antibody therapy for BPAR

**Results**

- Gengraf® group significantly more likely to:
  - Have BPAR episode (39% vs. 25%; $P\leq0.04$)
  - Have second BPAR episode (13% vs. 4%; $P\leq0.03$)
  - Receive an antibody preparation to treat the BPAR episode (19% vs. 8%; $P\leq0.02$)
  - Have higher degree of intrapatient variability for CsA $C_0$ concentrations as determined by %CV ($P<0.05$)
- No difference in graft or patient survival at 6 months between groups

**Conclusions**

Results suggest risk of developing BPAR during the first 6 months post-transplant are significantly higher with Gengraf® compared to Neoral®.

**Study Strengths**

- Endpoints based on more than pharmacokinetics
- High risk population: African American, cadaveric, de novo transplants

**Study Limitations**

- Retrospective design over two different time periods
- Dosing strategies not reported
- Goal $C_0$ achieved not reported
COMMON GROUND AND CONCLUSIONS

I. Overall Conclusions
   A. Generic substitution for brand name NTI immunosuppressants may result in concentration and $C_0$ changes
   B. While generic formulations typically lower medication costs, solid organ transplant failure is exceptionally costly
   C. Higher costs of brand name medications may prevent proper medication adherence due to affordability issues
   D. Definitive reports of clinical failures with generic NTI immunosuppressants has not been reported

II. Suggested Action
   A. Current literature does not support implementing changes in current FDA process or current legislation to facilitate utilization of generic NTI drugs
   B. Clinicians should educate patients to inform their physicians if labeling or appearance of immunosuppressant medications suggests substitution has occurred
   C. Pharmacist should use their best efforts to inform transplant teams when switch from brand to generic NTI immunosuppressant (or from one manufacturer to another) has occurred
   D. Heightened vigilance to adverse sequelae and closer therapeutic monitoring is advisable when substitution has occurred
      i. Ideally therapeutic drug levels would be measured before substitution has occurred and then one week after the switch
References

50. Wosinska M, Huckman RS. Generic dispensing and substitution in mail and retail pharmacies. *Health Aff* 2004;Suppl:W4-409-16.

51. Lake KD. Pharmacoeconomic and outcomes analyses in solid organ transplantation. *Graft* 2001;4:544-57


