Healthline VOLUME 36

Coram's Continuing Education Program

Current Issues in Transplantation – Brand versus Generic Immunosuppressants

The cost of prescription drugs in the United States is unsustainable. According to the U.S. Department of Health and Human Services Office of the Assistant Secretary for Planning and Evaluation (ASPE), prescription drug costs are projected to continue to rise – and to rise faster than the rate of health spending overall.[1] We continue to face double-digit growth overall in the costs of prescription drugs. Even the costs of generic formulations, while not double digit, are rising faster than inflation.[2,3]

Integral to our focus on healthcare spending stewardship is careful evaluation of appropriate cost-savings measures. One important area of focus is the safe and effective use of generic drugs in place of brand-name drugs. According to the U.S. Food and Drug Administration (FDA), an estimated half of all prescriptions in the United States today are filled with generic drugs.[4] In fact, brand-name manufacturers themselves produce an estimated 50% of generic drugs.[4]

Substituting generic formulations of brand-name drugs has the potential for significant prescription drug cost savings. For most drugs, there is no difference in clinical outcome when a generic version of a brand-name, or innovator, drug is used as opposed to the brand-name drug itself. However, for narrow therapeutic index medications, including immunosuppressive agents, the practice is more controversial given that so much is at stake. There is considerable concern among transplant teams and patients that generic and innovator immunosuppressants may not be equivalent to one another and that substitution places the patient at risk. Little data exists yet to provide a firm answer either way.

A generic drug is a therapeutically equivalent copy of a brand-name drug; identical to its brand-name counterpart in dosage form, strength, route of administration, quality, performance characteristics and intended use. FDA-approved generic drugs must meet the same inflexible standards as the innovator drug. Similarly, the manufacturing, packaging and testing sites must pass the same quality standards as those of brand drugs.

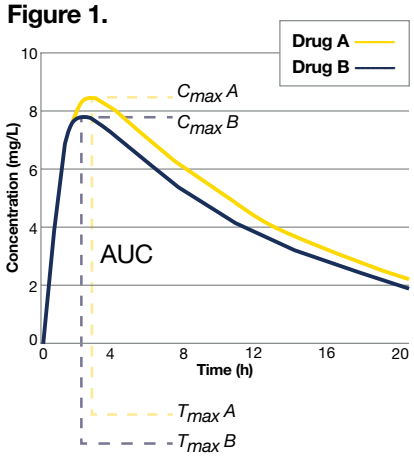
Potential differences, however, may exist in the excipients used in drug manufacturing. Excipients are inactive or inert ingredients (also studied and approved as safe by the FDA) that are added to the drug during the manufacturing process to, for example, keep tablets from sticking, improve taste and/or appearance, provide bulk, provide stability, and/or facilitate absorption. Drug products almost universally require the use of excipients. Therefore, while clinicians can be confident that the active ingredients in brand and generic drugs are the same, the excipients may not be. Will this create a different absorption profile? Again, probably not a significant risk with most drugs. But since blood concentrations are so important for critical dose drugs, can generic immunosuppressive and innovator products be automatically considered freely substitutable?

Determining Bioequivalency

Bioequivalence, or therapeutic equivalence, means that the active ingredient of two drug products has the same rate and extent of absorption. When it acts on its target, the brand-name and the generic formation should deliver the same amount of active ingredient to the target site.

Bioequivalence is typically measured pharmacokinetically. The drug is administered and the amount of the medication's active ingredient that is absorbed and detectable in the bloodstream is

Figure 1.

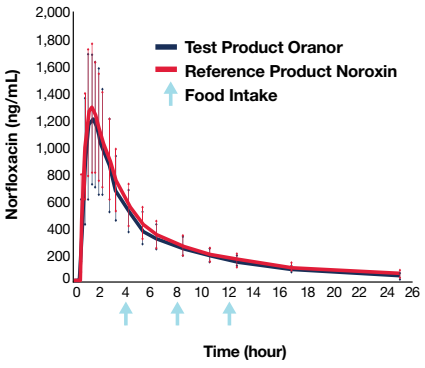


measured at specific time points after administration. See Figure 1 for an example. Calculated is the area under the curve (AUC), which represents a cumulative measure of drug concentration over time, i.e., how much has been absorbed. Also determined is the Cmax, the highest or maximum concentration detected.

For two drugs to be bioequivalent, the active ingredient must have the same extent (AUC) and rate (Cmax) of absorption, indicating that the same amount of each drug is delivered to the target site. If a generic drug formulation differs in one or both parameters, the generic formulation drug is not bioequivalent to the brand-name product.

Some degree of variability is acceptable when determining bioequivalency. This is important in its own right but even more important with critical-value medications. In bioequivalency studies, comparative drugs are tested in a group of persons. Given the natural differences between individuals, it makes sense that each person in the group would absorb medications uniquely. Both the brand and the generic will show variability among a population. Thus, the average values for AUC and Cmax are calculated, along with their degree of variability. Variability is a measure of how much the actual data vary from the average values. See example in Figure 2.

Figure 2.



The ratio of AUC and Cmax for both the test drug and brand-name drug are determined. A difference between test and brand-name drug of greater than 20% for AUC or Cmax or is considered significant by the FDA. Therefore, the lower limit of the AUC and Cmax ratios must be 80% of the average and, because the data are log-transformed, mathematically the upper limit of these ratios must be 125% of average. To take into account the inherent variability around the average values for AUC and Cmax, the FDA specifies that the ratios for Cmax and AUC, along with their 90% confidence intervals, must all fall within the 80%–125% window for a generic drug to be considered bioequivalent to a brand-name drug.

Interestingly, the acceptable range is narrower, at 90%–111%, in both Canada and Europe.[5,6]

Drug Costs–Brand versus Generic

There are a number of different contributors to the costs of drugs in the United States. The U.S. is the only country in the world that has "open pricing". Pharmaceutical companies can set any price they choose for their drugs and can increase the price of their products at any time. Developing new drugs and taking them to market is costly, with research costs that can take years to recoup and large marketing and advertising budgets. A manufacturer of that same drug in generic form does not incur all of those costs and thus the medication can be priced lower. In addition, the resulting competition helps lower prices. Generic substitution has the potential for significant cost savings for many stakeholders, especially patients.

This is true with transplant patients as well. Table 1 illustrates one example of price comparisons of several immunosuppressants, taken from one pharmacy at one point in time. The point of the table is not the actual costs, as costs may vary, for example, between pharmacies and insurance plans, and at any point in time. The point is the clear differences in prices of brand as compared to generic immunosuppressants.

Narrow Therapeutic Index Drugs

For most classes of drugs, since there is no difference in clinical outcomes between the generic and innovator preparations, generic substitution is not a concern. However, certain drugs have a narrow, or critical, therapeutic dose range. There is little difference between their effective and toxic doses and even small changes in dose or absorption can put patients outside of a therapeutic range — either to the side of toxicity or to the side of sub-therapeutic levels. In other words, there is little "wiggle room" between therapeutic and toxic dosing. The 80%–125% variability accepted for most drugs is too great for those with a narrow therapeutic window. Some examples are listed in Table 2.

Table 1

Example of Price Comparisons of Several Immunosuppressants*

	Brand	Generic
Gengraf®/Neoral® (cyclosporine) Dosing: 5 mg/kg/d 100 mg capsules #100 x 3	~$2,250	~$860
Prograf® (tacrolimus) Dosing: 0.05 mg/kg/d 1 mg capsules #100 x 1	~$490	~$65
Cellcept® (Mycophenolate mofetil) Dosing: 1 gm BID 500 mg tablets #100 x 1 #30 x 1	~2,400	~$115

*Based on initial dosing; full month supply for 70kg

Table 2

Narrow Therapeutic Index Medications

- Warfarin
- Levothyroxine
- Carbamazepine
- Lithium carbonate
- Digoxin
- Phenytoin
- Theophylline

Dosing for such drugs must be individualized and serum levels monitored.

Narrow Therapeutic Immunosuppressive Medications

Immunosuppressive drugs, specifically tacrolimus, cyclosporine, mycophenolate and, to some clinicians, sirolimus, are included in the narrow therapeutic index category. Substitution of any of these with generic formulations is controversial for many clinicians and patients, with a lack of data to clearly establish if the risk is real or theoretical.

Before approval, each generic drug must show bioequivalence to the innovator version in healthy adults. There is no requirement to determine bioequivalence or clinical efficacy specifically in transplant recipients. Clinicians may argue that the current criteria are not sufficient, as transplant patients often present with factors that could alter the pharmacokinetics of a drug, such as the presence of comorbidities and the fact that they are taking multiple drugs.

In a recent and significant review of the literature, no answer was clear. The authors concluded that high-quality data showing bioequivalence and clinical efficacy of generic immunosuppressants in solid organ transplants are lacking. While numerous studies have been published, the majority, according to these authors, had important limitations. As a result, there is insufficient evidence to provide reassurance that generics are equivalent to innovator immunosuppressants. But there is also no data to firmly suggest that generics are not equivalent and therefore unsafe.[7]

In a study presented at the 2015 (May) American Transplant Congress in Philadelphia, researchers conducted a prospective, blinded six-way cross-over study in 70 stable kidney and liver transplant patients. This study looked at the two most disparate generic formulations of tacrolimus—based on potency, purity and dissolution—to determine if they are bioequivalent to brand tacrolimus, Prograf®. No difference was found. The authors concluded that patients on brand-name tacrolimus could switch to generic without clinical consequence, assuming medication and monitoring compliance.[8] While important, this study was conducted in stable, low-risk patients. More research is needed in higher-risk populations, e.g., African-American or pediatric patients, as well as in comparing one generic to another.

Figure 3 illustrates bioequivalency of a non-narrow therapeutic index drug to two different generic formulations, generic A and generic B. Comparing either to the red line representing the brand-name drug, both A and B are within the acceptable range of variability and are thus bioequivalent to the innovator drug.

However, as illustrated in Figure 4, analyzing a narrow therapeutic index drug, neither generic A or generic B would be acceptable as therapeutically equivalent to the brand drug. The variability, while acceptable for most drugs, is too great for the critical dose drug and now presents itself as sub-therapeutic (A) or toxic (B). In transplant, however, what is the acceptable variability?

Figure 4 also introduces another challenge. Generic A and generic B are significantly different from each other, a result termed generic drift, so there is the added challenge of comparing generics to each other. This is critically important when considering a switch between generic formulations.

Figure 3.

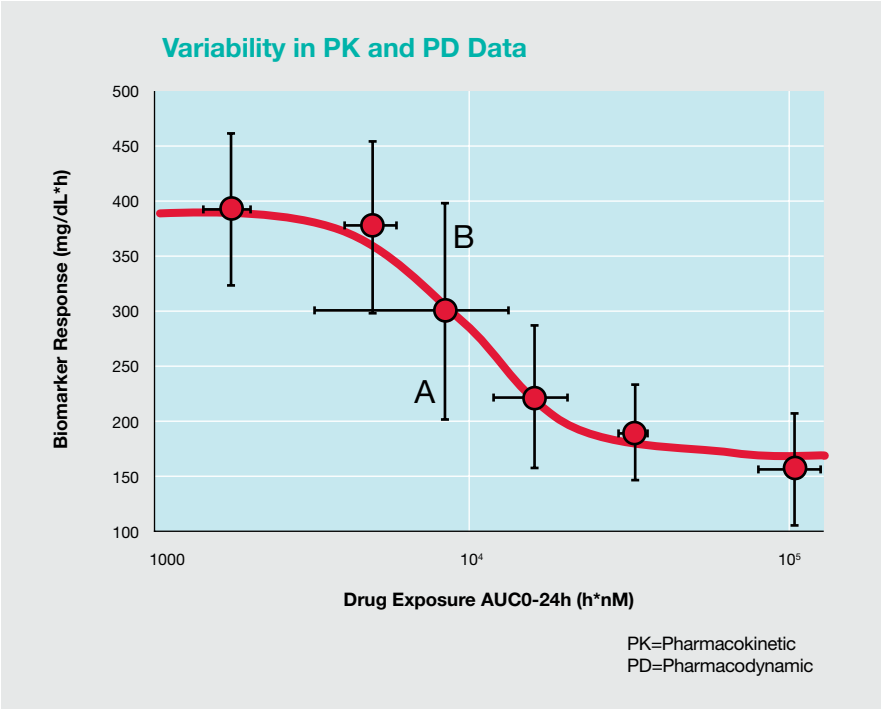
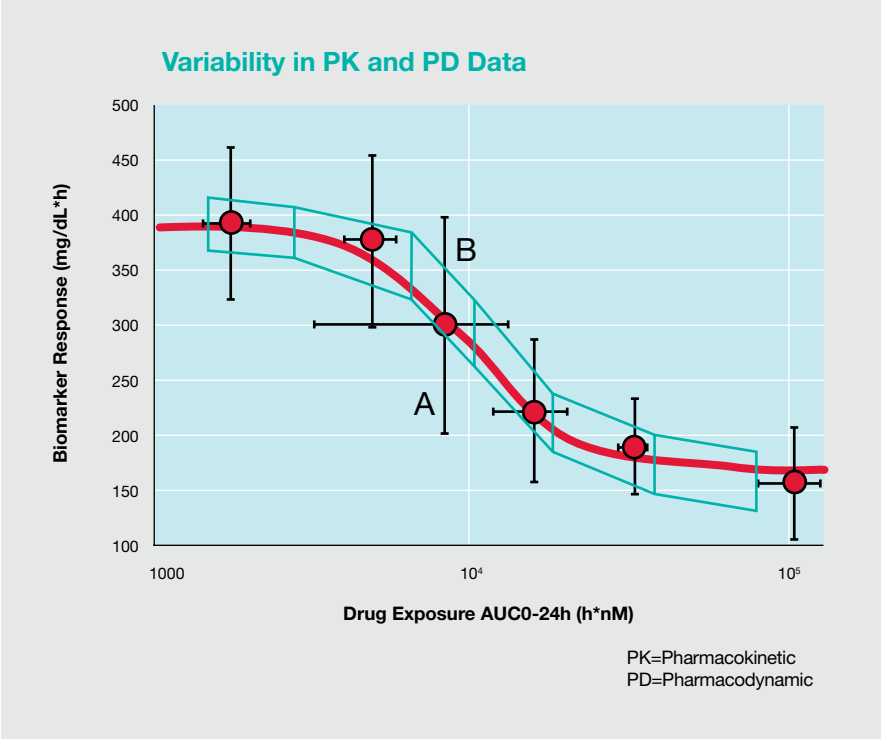


Figure 4.



Transplant Coordinator Perspective

Transplant coordinators express multiple concerns surrounding this topic. In a transplant coordinator poll, concerns were expressed about the impact of using or switching to generic formulations of immunosuppressant medications. Of concern were the increased availability of multiple generic immunosuppressive therapies, which has been associated with increased patient confusion and the potential for unintentional interruptions in therapy.

The coordinators identified the following as the top four contributors to patient confusion with their immunosuppressive therapy:

- Change in strength of the medications
- Switching from brand-name to generic medications
- Heavy pill burden
- Switching from one generic to another generic drug[9]

So, with a paucity of relevant data, what should be done now to minimize the risk? Actions worth investigating might include the:

- Development of regulatory safeguards such as prohibiting non-physicians (e.g., pharmacists and insurance company representatives) from authorizing substitutions of brand-name immunosuppressive agents with generics, or to minimize the risk of generic drift
- Requirement that a specific brand of immunosuppressant be specified on all prescriptions to avoid inadvertent switching
- Evaluation of the need for, and degree of, narrower variability parameters for these drugs
- Inclusion of stable and high-risk patients in research studies to assess bioequivalence
- Conduction of clinical and health economics studies to better inform clinicians, patients and payers of the risks and costs related to drug substitution
- Provision of patient education

Patient education specific to this topic is critical. Patients need to clearly understand the potential risk of taking a formulation of a drug different from the one originally prescribed. They must recognize the likelihood of increased blood monitoring to assure stability in case their absorption is different from one drug to the next. Patients must be able to recognize their specific formulation and thus be able to notice and report if a different one is dispensed. In some cases, a patient's health plan chooses which generic medication(s) it will cover, so it is important for both patients and families to learn which one they are likely to be prescribed.

Summary

It is well recognized that immunosuppressive medications are critical dose drugs, with outcomes highly sensitive to accurate dosing and absorption. While generic formulations of most medications are freely substitutable, a much greater challenge exists with critical dose drugs. Because of differences in rate and extent of absorption, generic formulations are not always bioequivalent either to the brand-name drug or to another generic of the same drug. Current recommendations call for more frequent serum level monitoring when a switch from brand to generic is made or if a switch from one generic formulation to another is made. Patients must be instructed about the risk of switching medications and about knowing which formulation they are prescribed. Any change in medication dispensed must be reported to the transplant team, both in the short and long term. ♦

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Self-Assessment Quiz:
Current Issues in Transplantation – Brand versus Generic Immunosuppressants

LEARNING GOAL

Gain an appreciation for the potential clinical and economic impact of using or switching to generic immunosuppressants and identify related precautions.

LEARNING OBJECTIVES

After reviewing this publication, each participant should be able to:

1. Differentiate brand versus generic drugs
2. Describe the challenges associated with critical value medications
3. Identify key issues associated with drug-switching

SELF-ASSESSMENT QUESTIONS

In the Quiz Answers section on the next page, circle the correct answer for each question. To obtain two (2.0) contact hours toward CE credit, the passing score is 100%. Return your Self-Assesment Quiz to Coram via email, fax or mail. See the next page for details on how to return to your quiz. Please allow approximately seven days to process your test and receive your certificate upon achieving a passing score.

1. **According to the Food and Drug Administration (FDA), currently an estimated ____% of all prescriptions in the United States are filled with generic drugs.**
   a. 25
   b. 30
   c. 50
   d. 60

2. **For the majority of medications there is _____ difference in terms of clinical outcome when a generic version is used in place of the brand drug.**
   a. No
   b. Little
   c. Significant

3. **FDA-approved generic drugs must meet the same strict standards as the innovator drug.**
   a. True
   b. False

4. **In order to be bioequivalent, the _____ must have the same rate and extent of absorption.**
   a. Active ingredient
   b. Excipient(s)
   c. Active ingredient and excipients(s)

5. **For two drugs to be bioequivalent, the active ingredient must have the same**
   a. Extent of absorption (AUC)
   b. Rate of absorption (Cmax)
   c. A and B

6. **Excipients may influence the extent and/or rate of absorption**
   a. True
   b. False

7. **Generic drift**
   a. Refers to the disparity in absorption between two generic formulations of the same drug
   b. Is critically important when considering a switch between generic formulations
   c. A and B

8. **Transplant coordinators identified the following as contributors to patient confusion with their immunosuppressive therapy:**
   a. Change in strength of the medications
   b. Switching from brand-name to generic medications
   c. Heavy pill burden
   d. Switching from one generic to another generic drug
   e. All of the above

9. **Because of differences in rate and extent of absorption, generic formulations are _____ bioequivalent either to the brand-name drug or to another generic of the same drug.**
   a. Always
   b. Not always
   c. Never

10. **Transplant patient education must include:**
    a. Information that more frequent monitoring may be necessary when switching from brand drug to a generic formulation
    b. Information that more frequent monitoring may be necessary when switching from one generic medication to another generic formulation of that medication
    c. How to recognize their specific formulation and report if a different one is dispensed
    d. All of the above
    e. A and C

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QUIZ ANSWERS

Fill in the key below with the correct answers to receive 2.0 Continuing Education credits.*

1. (a) (b) (c) (d)
2. (a) (b) (c)
3. (a) (b)
4. (a) (b) (c)
5. (a) (b) (c)
6. (a) (b)
7. (a) (b) (c)
8. (a) (b) (c) (d) (e)
9. (a) (b) (c)
10. (a) (b) (c) (d) (e)

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