Generic Drug Immunosuppression in Thoracic Transplantation: An ISHLT Educational Advisory

Patricia A. Uber, PharmD,[a] Heather J. Ross, MD,[b] Andreas O. Zuckermann, MD,[c] Stuart C. Sweet, MD,[d] Paul A. Corris, MD,[e] Keith McNeil, MD,[f] and Mandeep R. Mehra, MBBS[a]

The 1990s ushered in approval of several novel immunosuppressant drugs, including mycophenolate mofetil, tacrolimus, cyclosporine microemulsion, everolimus and sirolimus, with consequent improvement in clinical outcomes. Subsequently, the transplant community has been challenged with the development and introduction of generic immunosuppression drugs. These drugs represent a narrow therapeutic index and are thus classified as critical-dose agents. Sengai Gibon, a Japanese zen monk, wrote "Whether for life, whether for death—(it depends on) the right spoon-measure."[1] The purpose of this educational advisory is to provide an international perspective on regulatory and clinical concerns with generic immunosuppression medications in thoracic transplantation.

DEFINITIONS: CRITICAL-DOSE DRUGS AND NARROW THERAPEUTIC INDEX MEDICATIONS

Canada and the European Union catalog immunosuppression medications as "critical-dose drugs," characterized as those medications wherein comparatively small differences in dose or concentration lead to dose- and concentration-dependent, serious therapeutic failures and/or serious adverse drug reactions.[2,3] Such therapeutic consequences may be persistent, irreversible, slowly reversible or life-threatening, which could result in in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity and death.[4]

Similar in nature are narrow therapeutic index drugs, which are described as any pharmaceutical agent that has a less than 2-fold difference between the minimum toxic concentration and minimum effective concentration in blood. The United States FDA describes these products as having a less than a 2-fold difference in median lethal dose and median effective dose values, or a less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and that safe and effective use of the drug products require careful titration and patient monitoring.[5]

INTERNATIONAL REGULATION OF GENERIC MEDICATIONS

Regulating agencies around the world designate a generic preparation as either a pharmaceutically equivalent or pharmaceutical alternative product to the innovator (brand) product. Most countries insist that in order for a generic drug to be deemed pharmaceutically equivalent, they must contain the identical active ingredient to the innovator drug in the same strength, dose form and route of administration, and must be prescribed for the same therapeutic indication.[2,3,5,6] These products may differ in shape, color, inactive ingredients, release mechanism and packaging. Under these regulations, a generic drug may be considered therapeutically equivalent to the innovator drug if it is prescribed to patients under labeling conditions and exhibits similar clinical effect and safety profile, both of which are largely dependent on bioequivalence.

Bioequivalence is based on a comparison of mean pharmacokinetic parameters for brand and generic drugs, the area under the concentration–time curve (AUC), maximum concentration (C_{max}) and minimum concentration (C_{min}). The rate and extent of absorption can be determined either in vivo or vitro, depending on the regulating agency's requirements for each compound. Because immunosuppressant medications are characterized as critical-dose drugs or narrow therapeutic index medications, generic manufacturers must perform in vivo studies, often utilizing healthy volunteers.[2,6,7]

The pharmacokinetic studies commonly performed consist of a two-treatment crossover study design in 24 to 36 normal, healthy adults. Usually, both a single dose

From the [a]Division of Cardiology, University of Maryland School of Medicine, Baltimore, Maryland; [b]Division of Cardiology, Peter Munk Cardiac Centre, Toronto General Hospital, Toronto, Ontario, Canada; [c]Department of Cardiothoracic Surgery, Medical University of Vienna, Währinger Gürtel, Vienna, Austria; [d]Division of Allergy and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri; [e]Newcastle University and Cardiothoracic Centre, Freeman Hospital, Newcastle upon Tyne, UK; and [f]Queensland Centre for Thoracic Transplantation, The Prince Charles Hospital, Chermside, Brisbane, Queensland, Australia.

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Reprint requests: Mandeep R. Mehra, MBBS, Department of Cardiology, University of Maryland Medical Center, 22 South Greene Street, S3B06, Baltimore, MD 21030. Telephone: 410-328-7716. Fax: 410-328-4382. E-mail: mmehra@medicine.umaryland.edu

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Table 1. Pharmacokinetic Parameters and Study Conditions That Determine Drug Bioequivalence by Country

	AUC	C_{max}	Log-transformed parameters	Met in fasted and fed state	Steady-state required?
Canada	90% CI of relative mean AUC of test to reference should be between 90% and 112%	**90%** CI of the relative mean measured C_{max} of the test to reference should be between **80.0% and 125.0%**	Must be met, calculated from measured data and data corrected for measured drug content (percent potency of label claim)	Yes	Not unless warranted by exceptional circumstances; if required, the **90%** CI of the relative mean measured C_{min} of the test to reference should also be between **80.0% and 125.0%**
United States	90% CI of relative mean AUC of test to reference should be between 80.0% and 125.0%	90% CI of the relative mean measured C_{max} of the test to reference should be between 80.0% and 125.0%	Data are log-transformed prior to conducting statistical testing by ANOVA and calculating a 90% CI for each pharmacokinetic parameter; CI must be entirely within the 80% to 125% boundaries	May be required, standard high-fat diet is utilized; same parameters apply	For controlled released drugs or drugs with low levels with one dose; patients may be studied if the drug is considered dangerous with repeat doses in healthy volunteers; log-transformation C_{min}, C_{max} and AUC CI must be entirely within the 80% to 125% boundaries
EMEA zone (Europe)	90% CI for test/reference ratio should be within 80% to 125%	90% CI for test/reference ratio should be within 80% to 125%	Data are log-transformed prior to conducting statistical testing by ANOVA and calculating a 90% CI for each pharmacokinetic parameter; CI must be entirely within the 80% to 125% boundaries	Either (depending on drug)	Under special circumstances: 90% CI for test/reference ratio should be within 80% to 125%; however, if the single-dose study shows a very similar pharmacokinetic profile for test and reference (the 90% confidence interval for AUC is within 90 to 111), the requirement for steady-state data may be waived
Australia	90% CI of relative mean AUC of test to reference should be between 80.0% and 125.0%	90% CI of the relative mean measured C_{max} of the test to reference should be between 80.0% and 125.0%	Data is log-transformed prior to conducting statistical testing by ANOVA and calculating a 90% CI for each pharmacokinetic parameter. CI must be entirely within the 80% to 125% boundaries	No specific requirements	Not unless warranted by exceptional circumstances, such as controlled release drugs
Japan	90% CI of relative mean AUC of test to reference should be between 80.0% and 125.0%	90% CI of relative mean AUC of test to reference should be between 80.0% and 125.0%	Data are log-transformed prior to conducting statistical testing by ANOVA and calculating a 90% CI for each pharmacokinetic parameter; CI must be entirely within the 80% to 125% boundaries	No specific requirements	No specific requirements

CI, confidence interval; AUC, area under the curve; C_{max}, maximum concentration; C_{min}, minimum concentration.

of the test and innovator drug product are administered and blood or plasma concentrations are measured over time to determine the rate (C_{max}) and extent (AUC) of absorption of both products in a fasting or, occasionally, in a fed state as well. Pharmacokinetic parameters of interest are plasma AUC, calculated to the last measured concentration [AUC(0 − t)] and extrapolated to infinity [AUC(0 − infinity)], and the maximum or peak drug concentrations (C_{max}). Table 1 contains the pharmacokinetic parameters and regulatory require-

ments by various countries for consideration of bioequivalence.[2,5,6–9] A difference of >20% for each of the tests is considered to be significant and, therefore, undesirable for all drug products. Numerically, this is expressed as a limit of test-product average/reference-product average of 80% for the first statistical test (less bioavailable) and a limit of reference-product average/test-product average of 80% for the second statistical test (more bioavailable). By convention, all data are expressed as a ratio of the average response (AUC and C_{max}) for test/reference, so the limit expressed in the second statistical test is 125% (reciprocal of 80%). For statistical reasons, all data are log-transformed prior to conducting statistical testing. In practice, these statistical tests are carried out using an analysis of variance (ANOVA) procedure and calculating a 90% confidence interval for each pharmacokinetic parameter (C_{max} and AUC). The confidence interval for both pharmacokinetic parameters, AUC and C_{max}, must be entirely within the 80% to 125% boundaries just cited.

Regulatory agencies may require multiple-dose steady-state studies when controlled release dose forms are investigated or if the drug concentration from a single-dose study is too low to be measured by the available assays. Multiple-dose studies may, however, be considered too high risk for healthy volunteers in which case patients who have the underlying disease for which the medication was intended may be used. The same pharmacokinetic methods and standards are applied.

Some countries may allow for in vitro testing if more than a single strength of the innovator product is available for generic manufacturing. The vitro dissolution testing uses a specific methodology based on the solubility of the products, which is determined by the dose and intestinal permeability of that drug.[10] For example, tacrolimus 5 mg may be studied in vivo but the 0.5-mg and 1-mg doses may undergo in vitro dissolution testing for bioequivalence. Generally, 12 dose units of all strengths are tested to ascertain the rate and extent of availability during various testing scenarios that assimilate in vivo conditions.

SPECIAL CONSIDERATIONS

The use of healthy volunteers does not adequately represent the challenges faced in dosing immunosuppression in transplant recipients. Patients who have undergone transplantation exhibit challenges of chronic disease, experience effects of drug therapy on non-transplanted organs, are exposed to several medications that have interactions that alter the pharmacokinetic profile and have demonstrated extreme intrapatient variability of immunosuppressive medications. Other potential sources of intrapatient variation in bioequivalence include genetic factors, physiologic factors such as gastrointestinal transit time and pH, age, body composition, hormonal balance, non-compliance, smoking and chronologic factors.[8] Bioavailability may also be altered by co-administration with food and the effect may be largely formulation-dependent. A single-dose strategy may be inadequate to characterize all of these factors in medications that are considered critical-dose drugs or narrow therapeutic index medications with a large day-to-day variability in pharmacokinetic parameters even at steady state.

In addition thoracic transplant patients, who may be particularly vulnerable to adverse consequences of generic drug substitution, we must include those with high immunologic risk and history of treated allograft rejection. As in any condition, those who have traveled the less-than-desirable path secondary to frequent complications, such as rejection episodes or serious infections, are not patients in whom destabilization of a delicate balance is welcomed. These patients require a heightened vigilance to any change in their physical condition or changes in concurrent medication and immunosuppression once an appropriate cocktail of medications has been successfully established.

Unique clinical situations that deserve close attention are described in what follows.

Disease States Affecting Drug Absorption

Many patients who undergo thoracic organ transplant have gastrointestinal factors that alter the absorption of medications. For example, in patients with diabetes mellitus, cyclosporine absorption is decreased or delayed as compared with non-diabetic transplant patients, reflecting differences in gastric emptying.[11,12]

The gastrointestinal manifestations of cystic fibrosis also impede post-transplant management by causing significant variation in the rate and extent of absorption of orally administered immunosuppressive medications. Both tacrolimus and cyclosporine absorption are altered due to fat malabsorption, leading to a potential for rejection, and this has lead to the need for finding alternative ways to administer medications.[13,14]

Lactose intolerance affects about 70% of the world's population and can be seen in concert with inflammatory bowel diseases such as Crohn's disease. This may create altered absorption of drugs due to the presence of reduced transit time from diarrhea. The content of lactose, a readily used excipient in medications, can vary between innovator and generic formulations. Often the total amount of lactose in medications is not known and can actually reach a critical amount that may lead to symptoms in patients at risk. This was confirmed in a recent study that determined the milligram content of lactose in various medications used to treat gastrointestinal disorders. The investigators in that study discovered that some medications taken as prescribed could result in as much as 1-g or higher lactose ingestion.[15]

Ethnicity

African Americans and other populations with altered immunosuppression absorption patterns are typically underrepresented in bioequivalence studies and their differences marginalized with the use of healthy volunteers and statistical strategies that employ averages. This patient population has a highly variable immunosuppression drug absorption and exposure pattern, governed due to intestinal P-glycoprotein or polymorphisms of the cytochrome P450 system or other pharmacogenetic factors that await discovery. Drug interactions of coexisting medications may also alter the pharmacokinetics in these special populations. Therefore, the use of single-dose studies in volunteers not taking concomitant drugs that interfere with absorption, metabolism and clearance of immunosuppression may greatly underestimate the needs of this population.[16,17]

Genetic polymorphisms that affect drug absorption, metabolism and clearance have also been reported in various Asian populations. The presence of the CYP3A5(*)1 allele may be responsible for patients requiring a significantly higher dose of sirolimus or tacrolimus to achieve adequate trough concentrations.[18,19]

Dietary Interactions

Differing food interactions with innovator and generic products may have potentially serious consequences. Although specific product labeling may instruct patients to take the drug with or without food, considering the potential consequences of differing food interactions with products containing such drugs, bioequivalence should ideally be demonstrated under both fasting and fed conditions.[2] For example, the SangCya generic cyclosporine formulation initially demonstrated regulatory bioequivalence to Neoral; however, the product was recalled in the United States (in 2000) because cyclosporine concentrations were significantly affected by co-administration with apple juice, an interaction that was not seen with Neoral.[20–22]

Interactions With Concomitant Immunosuppressive Drugs

The current definition of bioequivalence does not require any testing on the impact of common drug interactions on drug levels or efficacy. The importance of concurrent medications in post-transplant patients should not be underestimated. There are multiple drug interactions that occur in this population, which involve the effect of one immunosuppressive agent on all other medications, including other immunosuppressants. The use of generic medications may or may not upset the fine balance currently in effect. Kovarik and colleagues[23] investigated the effect of two different cyclosporine preparations on sirolimus pharmacokinetics. They performed a single-dose crossover study of 28 healthy subjects who were randomized to receive sirolimus 5 mg as an oral solution with 250 mg Neoral cyclosporine as the innovator product versus the generic product, Gengraf cyclosporine. Gengraf significantly reduced the peak sirolimus blood concentration by 17% compared with Neoral cyclosporine ($p = 0.0003$). The AUC of sirolimus was significantly decreased by 11% in the presence of Gengraf as compared with Neoral cyclosporine ($p = 0.041$).

Children

Much of the concern regarding the use of generic immunosuppression in adults is heightened in pediatric transplant recipients because of age and developmental effects on medication pharmacokinetics. Most commercially available immunosuppressants do not currently have a labeled indication for pediatric use and safety, and efficacy data for young children are limited or absent. As such, it is unlikely that any bioequivalence testing in children is included in the generic approval process. Moreover, there are many developmental changes in physiologic factors that influence drug disposition in healthy infants, children and adolescents. These include the level and maturity of many enzymes involved in drug metabolism, such as cytochrome P450 enzymes, which may be reduced in infancy and later reach the level of activity seen in adults. Gastrointestinal pH and body composition change significantly from early infancy into childhood, thereby affecting drug absorption, distribution and degradation. Renal function and the capacity for tubular secretion do not reach the level of an adult until the child reaches 6 months to 1 year of age.[24] Thus, even without the added complexity of a generic preparation, age- and transplant-related changes in pharmacokinetics mandate close monitoring of immunosuppressive medications with narrow therapeutic indices.

PRACTICAL CONSIDERATIONS: NOTIFICATION OF SWITCHING AND SURVEILLANCE

Notification of Generic Substitution

Most countries have rules in place allowing dispensing authorities to substitute a bioequivalent generic product for the innovator drug (Table 2). This could create multiple problems, as there may be more than one generic formulation available. Therefore, the patient may be exposed to several different preparations during the course of therapy and each product may exhibit its own potentially different pharmacokinetic effects in concert with other medications that could create adverse outcomes.

Currently, no country has a system in place to notify the prescribing authority of the change from brand to generic medication, or generic to a different generic

Table 2. Prescribing and Dispensing Regulations Regarding Bioequivalent Generic Product Substitution by Country

Geographic location	Principal prescribing authority for first year post-transplant	Principal prescribing authority after 1 year post-transplant	Automatic generic substitution for medications allowed	Ability to specify "brand medically necessary" on prescription	Notification of change in manufacturer of immunosuppressive medication required
Canada	Any licensed MD can prescribe	Any licensed MD can prescribe	Pharmacy may automatically substitute without notification; it is customary, but not obligatory, to inform the patient if a medication is being substituted	Yes, however, under most drug plans, the patient would be responsible for paying the difference between the brand and generic cost	Not required
United States	Any licensed MD can prescribe; however, many transplant centers provided full care for first year	Any licensed MD can prescribe	Pharmacy may automatically substitute for drugs that are rated as therapeutically equivalent	Yes, however, under most drug plans, the patient would be responsible for paying the difference between the brand and generic cost	Not required
UK	Any licensed MD can prescribe	Any licensed MD can prescribe	Pharmacy may automatically substitute for drugs that are rated as therapeutically equivalent		Not required
EU	Depending on country and center	Depending on country and center	Pharmacy may automatically substitute for drugs that are rated as therapeutically equivalent	Yes (however, it might be questioned by insurance and confirmed by prescribing doctor)	Not required
Australia	Any licensed MD can prescribe	Any licensed MD can prescribe	Pharmacy may automatically substitute for drugs that are rated as therapeutically equivalent	Yes, however, under most drug plans, the patient would be responsible for paying the difference between the brand and generic cost	Not required

product. Due to the lack of such a systematic approach, the clinician's ability to monitor any changes depends on the patient's self-declaration to the health-care team.

Often, as Table 2 demonstrates, the health-care team performing the transplant is not always responsible for writing the prescription, and this adds another layer of complexity to the problem. Surveys of physicians have shown that there is little understanding of what determines bioequivalency of generic drugs.[25] It is therefore imperative that clinicians be required to educate themselves and develop programmatic direction on the use of generic drugs.

Surveillance Strategies

If the clinician changes the drug regimen of an established post-transplant patient to include a generic formulation, a heightened surveillance strategy is suggested. Pharmacokinetic monitoring of the generic medication and monitoring of levels of the other immunosuppression should be performed until stability is reached. Rejection surveillance, as well as monitoring for over-immunosuppression, should be initiated and continued until a new steady state has been established.

On the surface, it is perceived that use of generic immunosuppression would yield significant cost savings to the medical system. However, the direct savings potentially ensuing from such a strategy could be easily offset by additional surveillance therapeutic monitoring costs. Therefore, the cost-vs-benefit of generic medication in thoracic transplantation should be ascertained, keeping in mind the increased need for supplementary testing and monitoring to prevent adverse allograft-related outcomes.

SUMMARY RECOMMENDATIONS

Generic immunosuppression medications may offer an economic advantage, but it is imperative that clinicians

educate themselves about their pitfalls. We offer the following recommendations:

1. Clinicians should educate their patients to inform the coordinating center if a change in either the labeling or appearance of their immunosuppressive medications suggests that a generic drug substitution has occurred.
2. Clinical care coordinating centers must develop structured approaches for the education of all personnel with regard to use of generic immunosuppressants.
3. In unique clinical situations, where critical drug dosing represents a fine balance, caution should be exercised in the use of generic immunosuppression.
4. Heightened vigilance to adverse sequelae and closer therapeutic drug monitoring is indicated until a stable immunosuppression milieu can be established.
5. International advocacy efforts should be undertaken to develop routine clinical care coordinating center notification when generic drug substitution occurs.
6. International advocacy efforts should be undertaken to compel regulating agencies to approve only those generic immunosuppressants that have been studied under more appropriate circumstances, such as with concomitant interacting medications or in transplant recipients.

APPENDIX

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REFERENCES

1. Stumpf WE. The dose makes the medicine. Drug Discovery Today 2006;11:550–5.
2. Health Canada. Guidance for industry. Bioequivalence requirements: critical dose drugs (2006). Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/bio/critical_dose_critique-eng.php.
3. Verbeeck RK, Kanfer I, Walker RB. Generic substitution: the use of medicinal products containing different salts and implications for safety. Eur J Pharm Sci 2006;28:1–6.
4. Canada Food and Drug Regulations. Part C Drugs, Division I General, C.01.001. (1) Definition of serious adverse reaction. http://laws.justice.gc.ca/en/showdoc/cr/C.R.C.-c.870/bo-ga:l_C-gb:s_C_01_001//en#anchorbo-ga:l_C-gb:s_C_01_001.
5. Meyer MC. United States Food and Drug Administration requirements for approval of generic drug products. J Clin Psychiatry 2001;62(suppl 5):4–9.
6. Birkett DJ. Generics—equal or not? Austral Prescriber 3003;26:85–7.
7. Federal Regulations 21 CFR 320. Washington, DC: DHHS; 1998.
8. Palylyk-Colwell E, Jamali F, Dryden W, et al. Bioequivalence and interchangeability of narrow therapeutic range drugs. J Pharm Pharmaceut Sci 1998;1:2–7.
9. Guidelines for bioequivalence studies for generic products [in Japanese]; 2006. www.nihs.go.jp/drug/be-guide/GL061124_BE.pdf.
10. Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system. Washington, DC: FDA; 2000. http://www.fda.gov/cder/guidance/3618fnl.pdf.
11. Deierhoi MH, Haug M. Review of select transplant subpopulations at high risk of failure from standard immunosuppressive therapy. Clin Transplant 2000;14:439–48.
12. Schroeder TJ, Hariharan S, First MR. Variations in bioavailability of cyclosporine and relationship to clinical outcome in renal transplant subpopulations. Transplant Proc 1995;27:837–9.
13. Knoop C, Vervier I, Thiry P, et al. Cyclosporine pharmacokinetics and dose monitoring after lung transplantation: comparison between cystic fibrosis and other conditions. Transplantation 2003;76:683–8.
14. Reams BD, Palmer SM. Sublingual tacrolimus for immunosuppression in lung transplantation: a potentially important therapeutic option in cystic fibrosis. J Respir Med 2002;1:91–8.
15. Eadala P, Waud JP, Matthews SB, et al. Quantifying the 'hidden' lactose in drugs used for the treatment of gastro-intestinal conditions. Aliment Pharmacol Ther 2009;29:677–87.
16. Girnita DM, Webber SA, Ferrell R, et al. Disparate distribution of 16 candidate single nucleotide polymorphisms among racial and ethnic groups of pediatric heart transplant patients. Transplantation 2006;82:1774–80.
17. Girnita DM, Brooks MM, Webber SA, et al. Genetic polymorphisms impact the risk of acute rejection in pediatric heart transplantation: a multi-institutional study. Transplantation 2008;85:1632–9.
18. Miao LY, Huang CR, Hou JQ, et al. Association study of ABCB1 and CYP3A5 gene polymorphisms with sirolimus trough concentration and dose requirements in Chinese renal transplant recipients. Biopharm Drug Dispos 2008;29:1–5.
19. Macphee IA, Fredericks S, Mohamed M, et al. Tacrolimus pharmacogenetics: the CYP3A5*1 allele predicts low dose-normalized tacrolimus blood concentrations in whites and South Asians. Transplantation 2005;79:499–502.
20. Department of Health and Human Services, Food and Drug Administration to SangStat Medical Corp; withdrawal of approval on an abbreviated new drug application; cyclosporine. Federal Register 2000;65:75717.
21. First MR, Alloway R, Schroeder TJ. Development of Sang-35: a cyclosporine formulation bioequivalent to Neoral. Clin Transplant 1998;12:518–24.
22. Kovarik JM, Barilla D, McMahon L, et al. Administration diluents differentiate Neoral from a generic cyclosporine oral solution. Clin Transplant 2002;16:306–9.
23. Kovarik JM, Noe A, Wang Y, et al. Differentiation of innovator versus generic via a drug interaction on sirolimus. Eur J Clin Pharmacol 2006;62:361–6.
24. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology—drug disposition, action, and therapy in infants and children. N Engl J Med 2003;349:1157–67.
25. Banahan BF, Kolassa EM. A physician survey on generic drugs and substitution of critical dose medications. Arch Intern Med 1997;157:2080–8.