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The Myth of Bioequivalence

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Abstract

Generic medications can lead to significant economic and health-related savings in transplant recipients who require life-long immunosuppression to maintain survival of the allograft. Despite the growing number of generic immunosuppressants, there is significant concern over the process of approval by the FDA, particularly with regards to "narrow therapeutic range", in which demonstration of bioequivalence between generic and innovator drugs is carried out in normal, healthy volunteers. Bioequivalence between two agents in normal volunteers may not hold true among patient subpopulations that differ with regards to demographics, disease state, or the use of concomitant, potentially interfering medications. It is recommended that that the FDA considers replication of bioequivalence data by generic manufacturers of narrow therapeutic range drugs in transplant recipients. It is also recommended that certain safeguards and consistent policies be adopted to ensure that generic substitution is practiced in a responsible manner, including notification of the prescribing physician and patient when the pharmacy dispenses a narrow therapeutic range drug in a different formulation from the current medication. Therapeutic substitution should not occur unless the prescribing physician grants approval and institutes appropriate monitoring. Patients should be educated about the use of generics so that they recognize substitution and are allowed to participate in treatment decisions. **(Trends in Transplant. 2009;3:129-34)**

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Key words

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Introduction

Transplantation is the therapy of choice for patients with end-stage organ disease. More than two decades ago, the calcineurin inhibitor cyclosporine (CsA) was introduced, resulting in less acute rejection and improved graft survival compared with previous immunosuppressive regimens[1]. Although vital for organ survival, life-long immunosuppression is not without significant cost to the patient[2]. In the USA there are over 200,000 transplant recipients who require daily immunosuppressive therapy.

Generic medications offer patients the advantage of providing equivalent therapeutic

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efficacy at a lower cost to the patient, health-care system, and society. Lower-cost alternatives may improve adherence to therapies for patients who cannot afford innovator drugs, and provide an increased duration of therapy for those patients with capped medical benefits[3]. In 2008, generic drugs accounted for more than 63% of total prescriptions filled in the USA[4]. Despite the widespread availability of generic alternatives, substitution of these medications remains a topic of intense debate, particularly in the field of transplantation, in which survival of the organ, and in many cases the recipient, are at stake. At the core of the controversy is whether the current FDA standards regulating bioequivalence are restrictive enough to ensure that generic formulations of narrow therapeutic range drugs are clinically equivalent to their brand-name counterparts.

Generic approval process

According to the FDA, a generic drug is a product that compares to the innovator or reference drug product in dosage form, route of administration, strength, quality, safety, and performance characteristics. The generic drug must have the same intended use as the innovator product that serves as its prototype[5]. Unlike the approval process for innovator products, requiring manufacturers to include preclinical and clinical data establishing safety and efficacy of the active ingredient, the Drug Price Competition and Patent Term Restoration Act passed in 1984, more commonly known as the Hatch-Waxman Act, permitted the FDA to approve generic drugs without repeating safety and efficacy studies[6,7]. This is considered to be one of the most pivotal legislative moves on behalf of the generic drug industry as it eliminated the requirement for randomized trials to demonstrate clinical efficacy as long as bioequivalence was shown.

Bioequivalence refers to the absence of significant differences in the rate and extent to which active ingredients in pharmaceutical equivalents become available at the site of drug action in the body when administered under similar experimental conditions[8]. Bioequivalence studies aim to demonstrate that two pharmaceutical equivalents have similar pharmacokinetics. It is determined by evaluation of the area under the curve (AUC) and the maximum concentration of the drug (C_{max}). A generic product is considered to be bioequivalent to the innovator product if the 90% confidence interval of the mean AUC and the relative mean C_{max} is 80-125%. This criterion is the same standard used for testing the bioequivalence of branded products with reformulation or manufacturing changes. Bioequivalence studies typically enroll 24-36 healthy male adult volunteers, ages 18-50 years, in a single-dose, crossover design with the drug administered under fasting conditions. The C_{max}, time to reach C_{max}, and AUC are determined by taking multiple blood samples from individual patients. Based on the 90% confidence interval, if drug levels vary by more than 10%, failure to reach FDA criteria disqualifies a drug for a bioequivalence rating[8-10].

Critical-dose drugs

Despite determinations of statistical bioequivalence, there is still reluctance on the part of clinicians to substitute generic formulations for innovator drug products, particularly with regard to those having a narrow therapeutic range or “critical-dose drugs”. These drugs require careful patient monitoring and frequent dose adjustments as small changes in dose and/or blood concentration could potentially result in clinically important changes in drug efficacy or safety[11]. Consensus conferences held in the USA and Europe[12-14] raised nonequivalence

Table 1. Critical-dose drug characteristics

Narrow therapeutic range
Requirement for blood level monitoring
Dosing based on body weight or other highly individualized dosing requirements
Serious clinical consequences of overdosing (toxicity) or underdosing (lack of effect)
Steep dose-response relationship for either efficacy or toxicity or both

Adapted from Sabatini, et al.[12]

concerns over generic substitution of immunosuppressant agents, in particular cyclosporine and tacrolimus as these meet the criteria of critical-dose drugs (Table 1). The narrow therapeutic range has been well described with cyclosporine and the measurement of drug trough levels showing significant rates of acute rejection at low trough concentrations and toxic effects at higher concentrations[15]. Of note, there is significant overlap between toxic and nontoxic patients. Cyclosporine has also been noted to display significant inter- and intra-individual variations in drug absorption, distribution, metabolism, and elimination[16]. In an analysis by Kahan, et al.[17], it was demonstrated that those patients with significant intra-individual variability of cyclosporine exposure had an increase in the incidence of chronic rejection. The renal transplant recipients who were described as variable could not be discriminated from the less-variable cohort based on demographic, clinical, or laboratory characteristics, but only by serial pharmacokinetic profiling, further emphasizing the role of frequent drug monitoring of critical-dose drugs[17]. There are also formulation-dependent bioavailability issues to consider with cyclosporine. Depending on the delivery system, there can be significant differences in the peak concentrations, rate of absorption, and area under the concentration curve[18,19]. For example, Curtiss, et al. examined differences in bioavailability between the oral solution formulation of Sandimmune® (Sandoz Pharmaceuticals) and the soft gelatin capsule formulation in a randomized crossover study of 20 maintenance renal transplant recipients shown by screening pharmacokinetic profile to be poor absorbers of cyclosporine. Significant differences were noted, with an average 38% greater peak and 11% greater total exposure for the soft gelatin capsule as compared to the oral solution[20].

Impact of generic formulations on clinical outcomes

As mentioned above, bioequivalence is determined from single-dose studies in small numbers of fasting, healthy, normal volunteers, often homogeneous in characteristics. It is important to note that bioequivalence does not take into account potential drug interactions, disease interactions, or patient variables. Also, single dosing in contrast to chronic administration does not create the steady state conditions necessary for accurate evaluation of bioequivalence. It has been suggested that pharmacokinetics in healthy volunteers may not accurately reflect those in transplant recipients, particularly with critical-dose drugs. One must also recognize that bioequivalence alone does not demonstrate therapeutic equivalence, which is what providers desire and patients expect. Hibberd, et al. recently compared a generic formulation of cyclosporine, Cysporin (Mayne Pharma Limited) to the innovator drug, Neoral® (Novartis Pharmaceuticals) in a stable cohort of renal transplant recipients and found that although bioequivalent, the pharmacokinetics differed, with the rate and extension of absorption of the generic product being less and slower[21]. This could potentially have significant clinical consequences if the patient was switched to the generic drug without the physician being aware and ordering repeated CsA monitoring.

In a single-center retrospective review of patients initiated on Neoral® vs. Gengraf® (Abbott Laboratories), it was noted that the Gengraf® patients were significantly more likely to have a biopsy proven acute rejection episode during the first six months post-transplantation and also to have a second biopsy proven acute rejection episode[22]. It was interesting to note that the coefficient of variation of mean 12-hour CsA trough concentrations was significantly higher for Gengraf®, particularly in African American patients. These factors, in particular increased coefficient of variation, have been shown to be associated with increased rates of chronic rejection. Kahan, et al. examined individual pharmacokinetic parameters in 204 patients treated for up to five years and found that a greater than 20% coefficient of variation of cyclosporine bioavailability was a risk factor for the occurrence of chronic rejection[23]. The Collaborative Transplant Study group has demonstrated that patients who received Neoral® as compared to Sandimmune® had superior four-year graft survival[24].

Healthcare costs

Ultimately, the clinical outcomes of switching from innovator drug to generic, in particular with regards to cyclosporine, can affect total healthcare costs with re-hospitalization, management of acute rejection, and possibly graft failure with return to dialysis and retransplantation. An economic analysis performed on the previously mentioned study by Kahan, et al.[17] found that those patients with less-variable CsA exposure had significantly lower healthcare costs as compared to those with more-variable CsA exposure ($48,789 vs. 60,998 over five years; $p < 0.01$). Most recently, we have assessed overall healthcare costs for *de novo* renal transplant recipients receiving branded vs. generic CsA formulations[25]. In a cohort of 227 recipients, total healthcare costs were 46% higher for patients receiving generic vs. branded CsA. For the average patient, predicted costs were $36,443 for generic CsA and $31,494 for branded CsA, representing a statistically significant difference of $4,949. The difference in cost for this particular cohort was primarily driven by cost associated with immunosuppressants other than CsA, suggesting that the cost saving associated with generic CsA is outweighed by the need for more immunosuppressants to maintain the transplanted kidney.

Recommendations for drug substitution in transplantation

As the patents for Prograf® (Astellas Pharma) and CellCept® (Roche Pharmaceuticals) expire and generics for these innovator drugs become available, one can draw on the lessons learned from cyclosporine. We are all aware that noncompliance is a prominent cause of graft failure, with a portion of the noncompliance attributable to the inability to afford the cost of expensive immunosuppressive medications on the part of the patient[26]. If savings resulting from the use of generic immunosuppressive medications are passed on to payers and consumers, then the use of generic alternatives has the ability to improve compliance and reduce out-of-pocket expenses.

In prescribing generics, particularly those new to the market, one must use both common sense and caution. Currently, most regulations are to ensure that generic substitution is practiced in a responsible manner and made and enforced at the state level[11,27]. Those regulations vary from state to state, which has led to inconsistency in substitution practices and may cause confusion when trying to evaluate on a broad level.

Table 2. Recommendations for the use of generic immunosuppressant drugs

The healthcare provider should educate the patient about generic drugs and should include the patient in the decision of whether to switch drugs.
The pharmacist should inform the prescribing physician and patient whenever a prescribed immunosuppressive drug is to be switched.
Physicians should seek information about the bioequivalence data for the agents they prescribe and should be able to exercise their option to request substitution not be made if there is concern about maintenance of consistent drug regimens or about bioequivalence of generic drugs.
Patients should be taught how to identify the prescribed dosage form, and they should alert the physician if a substitution is made.
The FDA should require that the appearance of all medications be unique and easily identifiable to help patients distinguish among drug products.
Because of potential consequences arising from differences in bioavailability or intra-subject variability with different products of critical-dose drugs, physicians should consider instituting appropriate monitoring whenever a patient is switched from one formulation to another.
The healthcare team should report adverse events with innovator and generic drugs to the FDA and the drug's manufacturer and document the information in the patient record.

Adapted from Alloway, et al.[13] and Sabatini, et al.[12]

A major concern is that a prescribing provider may not be aware of a switch by the pharmacist to a generic. In such instances, the physician would be unaware of the possible consequences of the switch. Another concern is that the patient is not involved in the decision to switch medications. Based on these issues and to ensure safety and consistency in practice, recommendations were set forth by several organizations[12-14] (Table 2). Most important is that the physician and patient be made aware of the substitution so that appropriate follow-up and drug monitoring can take place.

The FDA has acknowledged that there may be issues in generalizing results obtained in healthy volunteers to specific subgroups of patients, particularly with critical-dose drugs. For such patients, the products might not be bioequivalent, even though these agents can be bioequivalent for most of the population. Although it would be difficult to establish bioequivalence in every potential patient subgroup, it is recommended that the FDA consider individualizing the bioequivalence testing for certain generic formulations, in particular those with a narrow therapeutic range.

Conclusions

As generic formulations for immunosuppressant medications become more widely available, it is important for providers to have a clear understanding of the approval process and how bioequivalence is determined. One must know that the pharmacokinetic profiles of critical-dose drugs may be different among transplant patients as compared to normal, healthy volunteers. These differences may lead to unanticipated differences in clinical response when generics are substituted for innovator drugs in this population. As a result, certain safeguards should be adopted to prevent poor outcomes from inappropriate generic substitution. It has been recommended that the FDA consider more stringent standards for bioequivalence with regards to critical-dose drugs, requiring drug manufacturers to

conduct replicate studies of intra-subject variability and subject-by-formulation interactions in addition to conventional bioavailability studies. It is also suggested that the generic manufacturer show bioequivalence in target populations in which the innovator drug has shown substantial pharmacologic variation.

Obviously, the cost-related benefits with regards to generics, including potential for improved compliance, are welcome, but the provider and patient must be aware of substitutions by the pharmacy to ensure that appropriate monitoring is instituted and patients are managed accordingly. Only with consistent substitution practices adopted by all parties can one ensure the safe and effective use of generic drugs in the transplant population.

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