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Generic Immunosuppressants

By David Lewino RN, CCTC, CPTC

Generic formulations of brand name drugs have been approved by the FDA for over 20 years (1). In fact, generic drugs account for most of the pills currently dispensed in United States pharmacies. Use of these alternatives saved American consumers $121 billion dollars last year alone, according to the Generic Pharmaceutical Association. Many insurance companies now offer coverage only on generic medications, as a cost conserving measure.

Immunosuppressant medications are extremely costly. Because they are essential for the preservation of allografts in transplant patients, the introduction of generics, though a welcome relief from the cost burden, was of great concern. The first major immunosuppressant to become generic was cyclosporine in May, 2000. At that time there were differing opinions on the significance of this release. Within a matter of weeks several versions of cyclosporine were available: for example, Eon, Pliva and Gengraf to name a few. The competition amongst the manufacturers was vigorous. A pharmacy might offer one brand one week, only to get a better price from a different manufacturer the next week and switch brands accordingly. There were stories of patients being given different strengths from different manufacturers in a single prescription. Though generic drugs need, by definition, to be bioequivalent to the brand name drug, they can still differ in shape and color. Tablets may have different scoring configurations. They may also have different expiration dates. It was a confusing time for patients and health care providers alike. The recent release of a generic tacrolimus (Prograf), as well as seven different versions of mycophenelate mofetil (CellCept), brings back memories of the confusion experienced in the first round with cyclosporine. It is likely to keep transplant physicians, pharmacists and nurses busy, as they attempt to ensure that their patients stay healthy.

As we start down this road again it may be helpful to look back on what we have learned from the cyclosporine experience. Although use of generic medications is well established and plays a crucial role in keeping health care costs down, medical professionals still have concerns about their use in some patient populations, including transplant recipients.(2-5) We know that transplant medications are critical to ensuring that the patients maintain their allografts. We also know that there is a narrow range between toxicity and under dosing of these medications. Concerns remain about how the FDA (Food and Drug Administration) currently defines bioequivalence and whether these requirements are appropriate for the approval of generic formulations of Narrow Therapeutic Index (NTI) or critical dose drugs (2). Drugs are regarded as having a NTI if there is only a small difference between plasma concentrations that achieve efficacy vs. those that will result in toxicity. While some variations in concentration may be “acceptable” in antibiotic or statin therapy, it is felt

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In 1999 David joined Stadtlanders Pharmacy (now known as Pharmacare) as Western Regional Manager for Sales, in the Transplant Division. It was during this period that the first generic Cyclosporine was released. In 2001 David returned to UC San Diego as a kidney transplant coordinator, obtaining his Certified Clinical Transplant Coordinator (CCTC) credential in 2004. David is currently a pre-Transplant Coordinator at the UC San Diego Center for Transplantation. He is also a member of the Astellas Speaker Bureau .

that in the case of immunosupression potential variations are unacceptable. Patients on immunosuppressive drugs require blood level monitoring. They have highly individualized dosing requirements, and there are serious consequences for overdosing or under dosing.

When seeking approval of a new drug, the pharmaceutical company must submit a New Drug Application (NDA) to the FDA. An NDA must include clinical studies demonstrating that the new drug is clinically safe and effective for its proposed indication(s), and whether the benefits of the drug outweigh the potential risks. Therefore, many preclinical (animal) and clinical (human) studies need to be conducted to collect the required safety and efficacy data. Completion of these studies can take several years, require enrollment of many thousands of patients, and considerable investment on the part of the pharmaceutical company (6).

Alternatively, the generic drug company is only required to submit an Abbreviated New Drug Application (ANDA). As the name implies, the information the sponsor is required to submit is abbreviated. The ANDA process does not require the generic company to submit preclinical or clinical data establishing the safety and efficacy of the active ingredient of the generic, because these data were previously submitted during the approval process for the innovator/ brand drug. Generally, only a single pharmacokinetic clinical study in healthy volunteers demonstrating bioequivalence to the innovator is required (7). A typical pharmacokinetic bioequivalence study involves measuring the drug pharmacokinetics (levels of drug in the blood) after the administration of an oral dose of both innovator and the generic formulation to 24 to 36 healthy adult volunteers. No clinical trials in the actual patient population are required by the FDA to validate these results(8).

Critics of this process believe a single dose study in healthy individuals does not capture many of the issues facing transplant recipients, such as medication interactions, genetic factors,GI motility,age,diabetic status, smoking and dietary interactions. For example, SangCya a generic cyclosporine formulation initially demonstrated regulatory bioequivalence to Neoral, the brand name drug. However the product was recalled in the United States because cyclosporine concentrations were significantly affected by co-administration with apple juice, an interaction that was not seen with Neoral.

In May 2000, the FDA approved Gengraf, a generic version of the innovator brand Neoral (cyclosporine) capsules. In an effort to validate whether the bioequivalence of Neoral and Gengraf translated into the same clinical efficacy and safety, several studies were conducted. In 2002 (Roza and colleagues) (9) and 2003 (Carnhahan and Cooper) (10) assessed conversion from Neoral to Gengraf in 50 and 41 stable renal transplant patients, respectively.The results of these studies indicated that similar plasma drug concentrations were achieved both before and after the switch to Gengraf and NO dose adjustment was required.

However in 2006 (Qazi and associates) (11)evaluated 82 stable kidney patients, 73 of whom were randomized to conversion from Neoral to Gengraf. In this study 20% of the patients on Gengraf required dose adjustment. Those remaining on Neoral required no dose adjustment. In 2005 (Taber et al)(12) assessed 188 de novo kidney transplant patients who received either Neoral or Gengraf. Patients receiving Gengraf experienced a significantly higher incidence of acute rejection. In addition, higher intrapatient variability was reported in CsA blood levels in the Gengraf treated patients.

Both the American Society of Transplantation (AST) and the National Kidney Foundation (NKF) independently convened experts and released position statements on the substitution of immunosuppressant agents. The availability and use of generic formulations was welcomed and endorsed because of the potential economic benefits. However based on concerns previously mentioned in this piece recommendations on

safety and efficacy were provided. The cyclosporine experience has also taught us that generic immunosuppressants will work their way into our patients' pharmacy profile. Managed care, assistance programs and financial concerns will remove choice for many of our patients. Therefore it is imperative we develop a strategy to provide safe and cost effective care to our patients.

When making a prescribing decision for an immunosuppressant patient welfare must be the preeminent concern. Is the potential for variations in blood levels appropriate for a particular patient? Is that patient high risk, i.e. second transplant (15% of patients on the national waiting list have received a prior transplant), African American or with a history of fluctuating blood immunosuppressant levels? Additionally, since a prescription can be valid for 12 months, thorough patient education is essential. We must:

• Inform patients that multiple medications are available.

• Educate patients to be able to recognize his/her prescriptions, the names of the drugs, the dosages, and the formulations (look) of the medications.

• Prior to leaving the pharmacy with their medications, encourage patients to verify that the medication dispensed is indeed the medication prescribed.

• As always, stress the importance of medication adherence and encourage patients to call the transplant program with ANY questions.

It is clear that the use of generic medications will continue to grow. The transplant team will often not be contacted when the decision to substitute a generic medication for a name brand is made. Whenever a patient is started on a generic immunosuppressant, blood levels during transition can be very helpful and should be obtained. Finally, if the there are concerns that generic substitution may not be appropriate for a particular patient or group of patients, the physician must protect his or her decision by writing "Dispense as Written" on the prescription and be prepared to engage the patient's insurance company with supporting data.

COMPONENTS OF WRITTEN PRESCRIPTIONS

PATIENT'S FULL NAME AND ADDRESS

PRESCRIBER'S FULL NAME, ADDRESS, TELEPHONE NUMBER

PRESCRIBER'S DEA AND NPI NUMBERS

DATE OF ISSUANCE

DRUG NAME, DOSE, DOSAGE FORM, AMOUNT

DIRECTIONS FOR USE

REFILL INSTRUCTIONS

PHYSICIAN SIGNATURE

DISPENSE AS WRITTEN (DAW) OR GENERIC PERMITTED NOTED ON PRESCRIPTION

BIBLIOGRAPHY:

1. Food and Drug Administration (FDA)/Center for Drug Evaluation and Research (CDER).Abbreviated New Drug Application (ANDA) process for generic drugs.

http:www.fda.gov/cder/regulatory/applications/ANDA.htm

2. Sabatini S, Ferguson RM, Helderman JH, Hull AR, Kirkpatrick BS, Barr WH. Am J Kidney Dis. 1999;33(2):389-397.

3. Alloway RR, Isaacs R, Lake K, et al. Am J Transplant. 2003;3(10):1211-1215.

4. Meredith P Clin Ther. 2003;25(11):2875-2890

5. Johnston A,Holt DW.Transplant Proc.1999;31(3):1649-1653.

6. FDA/CDER. New Drug Application (NDA) process.

http://www.fda.gov/cder/regulatory/applications/NDA.htm.

7. FDA/CDER. Abbreviated New Drug Application (ANDA) process for generic drugs.

http://www.fda.gov/cder/regulatory/applications/ANDA.htm.

8.FDA/CDER.Approved Drug Products with Therapeutic Equivalence Evaluations.28th ed.

http://www.fda.gov/cder/ob/docs/preface/ecpreface.htm.

9. Roza A,Tomlanovich S,Merion R,et al.Transplantation. 2002;74(7):1013-1017.

10. Carnahan W, Cooper TY. Transplant Proceedings.2003;35(4): 1308-1313.

11.Qazi YA, Forrest A, Tornatore K,Venuto RC,Clin Transplant.2006;20(3): 313-317.

12.Taber DJ,Baillie GM, Ashcraft EE,et al.Transplantation.2005;80(11):1633-1635.

13.Alloway RR, Isaacs R, Lake K, et al.Am J Transplant.2003;3(10):1211-1215.

14. Sabatini S, Ferguson RM, heldman JH, Hull AR, Kirkpatrick BS, Barr WH. Am J Kidney Disease 1999:33(2):389-397.