Generic Immunosuppressants in Hematopoietic Cell Transplantation

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SCOPE OF THE ISSUE

Successful immune suppression and modulation is a cornerstone in the hematopoietic cell transplantation (HCT) process. Only a limited number of active immunosuppressive compounds are commonly used in HCT. Despite the relatively limited number of HCTs performed in the United States each year, there is a multimillion dollar market for pharmaceutical immunosuppressants, given the more extensive use of these drugs in solid organ transplantation. As such, an active generic immunosuppressant industry has evolved over the past few years.

Clinical studies comparing outcomes from the use of brand-name and generic immunosuppressant drugs in HCT have not been performed, and the use of generic immunosuppressants has not been recommended or discouraged by the American Society of Blood and Marrow Transplantation (ASBMT). In September 2009, the ASBMT’s Executive Committee convened a Task Force to evaluate the use of generic immunosuppressants in HCT. The Task Force examined issues of drug bioequivalence, drug safety, and pharmacoeconomics in HCT and prepared this report by consensus. Opinions were solicited from members of the brand-name pharmaceutical industry, the generic pharmaceutical industry, and the insurance industry, as well as university-based healthcare economists and researchers.

GENERIC IMMUNOSUPPRESSANTS

Many different pharmaceutical companies produce generic immunosuppressant agents. At the time of this writing, there are at least 8 generic versions of mycophenolate mofetil (CellCept; Roche, San Francisco, CA) and 3 generic versions of tacrolimus (Prograf; Astellas, Deerfield, IL) on the market in the United States (Figure 1). Numerous generic versions of cyclosporine have been marketed for years, and the transplantation community has long used generic versions of prednisone without issues.

A generic drug product is one that is comparable to a brand name drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use [1]. Generic drugs contain active ingredients that are identical to the corresponding brand-name formulations; sometimes the active compound is even purchased from the same chemical manufacturer. The differences between brand-name and generic drugs lie in the excipients included in the formulations, as well as in the physical composition of the drug in pill, liquid, or i.v. formulations.

Generic medications are approved by the Food and Drug Administration (FDA) through a process known as an Abbreviated New Drug Application (ANDA). The key to the ANDA approval process lies in...
bioequivalence testing. Bioequivalence testing for generic drugs is governed by the Drug Price and Competition and Patent Term Restoration Act of 1984 (also known as the Waxman-Hatch Act), an update to the ANDA process initially promulgated in 1970 (described in §21 CFR Parts 314 and 320). Evidence of bioequivalence is often, if not exclusively, demonstrated in normal volunteers, whereby the pharmacokinetics (area under the curve [AUC] and peak concentration [C\text{max}]/time to peak concentration [T\text{max}]) of single or multiple doses of the generic compound are compared with the brand-name compound in a crossover fashion. Generic manufacturers do not need to recapitulate any phase I-III clinical tests that have already been performed to demonstrate the safety and efficacy of the brand-name drug to the FDA [2].

The statistical requirements for bioequivalence, expressed as an average AUC or C\text{max} ratio of the generic compound to the brand-name compound, allow up to 20% variability between brand-name and generic compounds. Thus, using 90% confidence intervals, a generic product may have pharmacokinetic properties anywhere between 80% and 125% (the inverse of 80%) of those of the parent compound to fulfill

### Figure 1.
Images of commercially available preparations of mycophenolate mofetil and tacrolimus, where available.

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<th>Manufacturer</th>
<th>250 mg Capsule</th>
<th>500 mg Tablet</th>
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<td>Roche</td>
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<td><strong>Generic Mycophenolate Mofetil</strong></td>
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<td>Mylan / UDL</td>
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<th>Manufacturer</th>
<th>0.5 mg capsule</th>
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<td>Astellas</td>
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<tr>
<td><strong>Generic Tacrolimus</strong></td>
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<td>Dr Reddy’s Laboratories</td>
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<tr>
<td>Mylan</td>
<td>Hard-shell gelatin capsule with a light orange opaque cap and a gray opaque body filled with white to off-white powder, axially printed with MYLAN over 2045 in black ink on both the cap and the body</td>
<td>Hard-shell gelatin capsule with a light blue opaque cap and a gray opaque body filled with white to off-white powder, axially printed with MYLAN over 2046 in black ink on both the cap and the body</td>
<td>Hard-shell gelatin capsule with a rubine red opaque cap and a gray opaque body filled with white to off-white powder, axially printed with MYLAN over 2047 in black ink on both the cap and the body</td>
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<td>Watson</td>
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the requirements for bioequivalence [3]. This wide equivalence range represents the total variability of the test subjects and is influenced by intersubject variability during the testing phase, as well as the variance of the bioanalytical assays used to measure pharmacokinetics.

The FDA recently published a retrospective analysis of the bioequivalence testing of oral agents subjected to the ANDA approval process over the last 12 years. In this analysis of 2070 bioequivalence assays, the average differences in $C_{\text{max}}$ and AUC were $4.57\% \pm 3.59\%$ and $3.17\% \pm 2.69\%$, respectively. These variances were slightly lower when 1788 immediate-release–only formulations were examined ($4.43\% \pm 3.50\%$ and $3.15\% \pm 2.66\%$, respectively). The FDA found that $97.8\%$ of the immediate-release formulations had AUC differences of $<10\%$ [4].

Two recent systematic reviews and meta-analyses in randomized controlled trials found no evidence of a superiority of brand-name drugs over generic drugs in terms of efficacy in treating cardiovascular disease (including anticoagulation with warfarin) [5] or epilepsy [6].

Anecdotal evidence has emerged of patients experiencing different outcomes on switching from brand-name to generic products. Reports of possible clinical differences between brand-name and generic drugs are of particular concern for so-called “narrow therapeutic index” (NTI) drugs, in which the effective and toxic doses are separated by only a small difference in plasma concentration [7,8]. Some immunosuppressants also fall within this category of NTI drugs. It is important to note that in the United States, no special additional testing is generally required for NTI drugs, although additional testing is required by other regulatory agencies worldwide, such as Health Canada and the European Medicines Agency [9]. For immunosuppressants, however, the FDA has released guidance for the testing of food effects on both tacrolimus and sirolimus pharmacokinetics [10,11].

Given that the FDA approves generic drugs on the basis of their pharmacokinetic equivalency, in some circumstances, it may be important to demonstrate pharmacodynamic and efficacy equivalency as well. To date, however, neither brand-name nor generic pharmaceutical manufacturers have engaged heavily in these comparative trials.

**EXPERIENCE WITH GENERIC IMMUNOSUPPRESSANTS IN NON-HCT SETTINGS**

Given the lack of prospective or even retrospective analyses of outcomes related to the use of generic drugs in HCT, the Task Force reviewed the experience with other organ transplantation when formulating this position paper. Because of the long experience with alternate preparations of cyclosporine, that drug is not reviewed here.

**Tacrolimus**

The first generic tacrolimus preparation was introduced to the US market in late 2009, and as such, data on therapeutic conversion are limited. One small report of 4 pediatric patients inadvertently switched from brand-name to generic tacrolimus showed a significant drop in tacrolimus trough levels in one patient and acute rejection in another patient without a meaningful change in serum levels [12]. More important is a large multicenter study of generic tacrolimus conversion in solid organ recipients. A total of 102 conversions were reported, and $29\%$ of the patients required dosage titration. Approximately half of the patients required upward dosage titrations, and the other half required dosage reductions. Importantly, average drug costs fell by $53-$77 per month, but this did not account for the extra costs associated with increased therapeutic drug monitoring [13].

One prospective trial has compared the brand-name and alternative generic tacrolimus preparations in de novo renal transplantation. This trial demonstrated a near doubling of acute rejection episodes in the 222 patients randomized to the alternative preparation. Patients in the alternative preparation group had lower plasma drug levels compared with those in the brand-name group, and this was the variable most closely associated with acute rejection [14]. The alternative compound used in that study was not officially a generic drug as defined in the United States, because it had not been approved by the FDA. This and other alternative preparations of tacrolimus, all currently unavailable in the United States, have been shown to have different physiochemical properties than brand-name tacrolimus [15]. Other, nonrandomized analyses of alternative tacrolimus preparations have been published [16-18].

**Mycophenolate Mofetil**

Even though generic mycophenolate mofetil was introduced to the US market several years ago, the lack of a defined serum therapeutic range has made comparisons between brand name and generic compound less relevant. In a small series of patients with stable renal function after renal transplantation, 13 patients underwent pharmacokinetic studies after changing from brand-name to generic mycophenolate mofetil. All pharmacokinetic studies except 2-hour serum mycophenolic acid concentration were very similar in the brand-name and generic drugs. In addition, serum creatinine levels remained unchanged at 12 months after the switch [19].
GUIdelines from other professional societies on generic immunosuppressants

Other societies and professional organizations have issued their own recommendations regarding the use of generic immunosuppressants in their respective fields. The American Society of Transplantation has recommended further clinical trials of generic immunosuppressants in at-risk populations, specifically African Americans and pediatric patients, as well as education programs designed to encourage patients to inform their healthcare providers of the substitution of a generic drug for a brand-name drug [20]. Similar recommendations have been put forth by the International Society for Heart and Lung Transplantation [21]. The American Society of Nephrology does not have a published position on the topic; however, the National Kidney Foundation previously endorsed the use of generic immunosuppressant drugs, largely on the basis of the potential pharmacoeconomic benefits of these agents, while similarly calling for increased testing in transplantation subpopulations [22].

specific issues in HCT

In HCT, nearly all patients must contend with polypharmacy, and drug–drug interactions are often variable and unpredictable. These drug interactions exist between multiple immunosuppressants and supportive care medications, such as antifungal agents.

In at least one series in solid organ transplantation, differentiation between brand-name and generic cyclosporine was determined based on drug interactions with sirolimus [23]. This is relevant for medications such as tacrolimus, for which drug levels can be measured and dosage modifications made as long as the treating clinician is aware that a change in one drug is made. However, there currently is no mechanism to make clinicians aware of a therapeutic change in drug supply. The consequences of these dosage changes can be severe with respect to the level of the changed drug as well as with potential interactions with other drugs. Because generic drugs can have up to a 20% difference in pharmacokinetic properties with their brand-name counterparts (although such extreme differences were not routinely observed in the FDA study), a change from a generic drug with an anticipated pharmacokinetic absorption profile 20% lower than the brand-name drug to a generic drug with an anticipated pharmacokinetic profile 20% higher than the brand-name compound can lead to considerable differences in serum drug concentrations. Again, for drugs such as tacrolimus, as long as there is forewarning, close monitoring of serum levels can be initiated. However, for mycophenolate mofetil, for which drug level monitoring is not routinely performed and an optimal therapeutic window is not known, this change can have important clinical consequences. Both changes from a brand-name to generic formulation and from one generic formulation to another generic formulation can have these unanticipated consequences. Similar changes in therapeutic drug levels of supportive medications used in HCT can occur as well, and measurement of these drugs in the blood should be performed whenever possible.

One scenario of note relevant in HCT is the potential for a drug formulation change upon hospital discharge after transplantation. Although patients are likely to be provided a consistent formulation while hospitalized, the first prescription in the outpatient setting may be a different formulation. Because close drug-level monitoring is often maintained after transplantation, this is not likely to be associated with significant periods of time at either subtherapeutic or supratherapeutic drug levels, when measurable. In general, drug-level monitoring should be done at least once at approximately 1 week after a change in drug formulation.

Pharmacoeconomic and societal perspectives on the use of generic drugs in HCT

The Task Force considered several other positions when generating this report. These positions are from two distinct groups: drug manufacturers (of both brand-name and generic drugs) and the payers, a group comprising individual patients, insurance agencies, and the governmental healthcare support system.

From the patients’ standpoint, interventions that reduce out-of-pocket costs through a reduction or abatement of copayments for prescription drugs can promote adherence to chronic medication therapy [24]. In general, patients’ responsibilities for paying for prescription medications generally decrease with a change from brand-name to generic preparations, because a tiered formulary is common in insurance plans with prescription drug coverage. This was demonstrated in the recent trial of a planned switch from a brand-name to a generic drug in renal transplantation. Although not yet proven in HCT or organ transplantation, it has been demonstrated in other fields that copayments are significantly negatively associated with prescription medication adherence [25-27].

From the payers’ standpoint, any intervention that reduces costs associated with healthcare delivery without a change in patient outcomes is viewed favorably. A reduction in medication costs for the insurer (or governmental healthcare provider) could lead to greater coverage for services previously not covered for HCT patients as well as others in a similar situation. However, if switching to generic immunosuppressants
would require more intensive monitoring and/or lead to higher rates of adverse events, then these higher downstream costs could outweigh the initial cost savings associated with the use of generic drugs.

Pharmaceutical companies engaged in research to develop immunosuppressants for HCT stand to lose the most as bioequivalent generic competitors are approved and become more widely used. Manufacturers’ substantial research and development costs for future drugs are funded by revenues from currently marketed drugs, and thus the FDA has provided patent protection time periods meant to allow pharmaceutical companies time to recover the costs of drug development. On the other hand, market exclusivity leading to higher prices for brand name drugs should not be indefinite. Current legal limits on patent length suggest that patients should be allowed to enjoy enhanced access derived from the availability of lower-cost generic drugs after a certain period. It is beyond the scope of this Task Force to comment further on the issues of the duration of patent protection and cost recovery.

RECOMMENDATIONS OF THE TASK FORCE

1. **Patient education.** Patients should be educated on the possibility that their immunosuppressant medications could be altered in shape, size, or color. They should be educated that the FDA approves generic drugs as being bioequivalent to brand name products, and that there is no evidence suggesting that brand name drugs are superior. However, patients also should be encouraged to inform their healthcare providers of any change in their immunosuppressant drugs. Figure 1 should be provided to patients, made available on the ASBMT Web site for providers, and periodically updated when new drug formulations are approved for use.

2. **Consistent use of one drug formulation.** Providers should attempt to use only one formulation of an immunosuppressant drug, either consistently prescribing a brand name or a generic formulation, to reduce the possibility of changes in drug levels. Specifying which generic formulation in a prescription might not be feasible, however, given that a pharmacy is likely to only carry one generic formulation at a time. HCT physicians also should be encouraged to engage patients in conversations about their drug costs and the financial burden of these costs. If such a discussion suggests a concern for reduced adherence due to continued prescription of a more costly brand name formulation, then a monitored switch to a generic version should be encouraged.

3. **Enhanced monitoring after formulation changes.** Whenever patients change drug formulations, either between brand name and generic formulations or between two generic formulations, drug levels should be monitored, preferably after several half-lives of the drug have passed. In general, monitoring at least 1 week from the time of a formulation change should be sufficient.

4. **Clinical trials.** Clinical trials for equivalence, focusing on graft-versus-host disease and related outcomes, should be encouraged. Well-controlled observational trials also may provide insight into the question of the clinical equivalence of brand name and generic immunosuppressants. Individual drug levels, although relevant, are less important than trends and associations with poorer control of the adverse immunologic consequences of HCT.

5. **Analysis of true cost.** Although generic drugs may have lower retail costs and lower insurance copayments compared with brand-name drugs, studies of the true cost of these substitutions, including the costs associated with increased drug monitoring and the potential costs of adverse events associated with altered drug levels, should be performed to determine the financial implications of the use of generic immunosuppressants in HCT.

ACKNOWLEDGMENTS

The Task Force appreciates the input of Agnes Costello, PharmD, (Genzyme Corporation) and Marc Goshko (TEVA Pharmaceuticals), as well the administrative leadership of Thomas Joseph, MPS CAE.

**Financial disclosures:** Corey Cutler has received research support from Otsuka, Astellas, and Pfizer and serves on the Advisory Board or as a consultant to Otsuka, Astellas, Celgene, and Spectrum. Aaron Kesselheim serves as a consultant to the Alosa Foundation/Independent Drug Information Service. Scott D. Rowley serves on the Eusa speaker’s bureau and has equity in Pfizer and Johnson & Johnson. John R. Wingard has received honoraria from Pfizer, Astellas, Vical, and Merck. None of the other authors has any conflicts of interest to disclose.

REFERENCES


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