Conclusion

Comparison of the Bioequivalence of Generic Versus Branded Clozapine

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Clozapine, the first atypical antipsychotic, has been marketed in the United States since 1989. Its usage has been restricted to those patients with persistent psychotic or bipolar disorder who are considered treatment resistant and who are intolerant of standard antipsychotic therapies. Clozapine has also been found to be the least likely of the antipsychotics to worsen previously diagnosed tardive dyskinesia.[1] With the expiration of Novartis's patent for Clozaril in 1998, generic products have now begun to be marketed. Three generic drug manufacturers have obtained U.S. Food and Drug Administration (FDA) approval to market their clozapine formulations: Zenith Goldline Pharmaceuticals and Mylan Pharmaceuticals—whose drugs are currently marketed—and Geneva Pharmaceuticals—whose drug is currently unavailable in the United States. From an acquisition-cost basis, generic clozapine formulations are less costly than Clozaril, therefore making them highly attractive to public mental health systems. If generic substitution were simply a matter of cost, then doctors, patients, and caregivers would have few or no concerns. However, the decision to use generic products is complex, laden with both scientific complexity and patient and caregiver trepidation. Moreover, FDA approval of a generic drug as bioequivalent to the branded drug is not a guarantee of therapeutic and pharmacokinetic equivalence in all patients. Rather, it is a statement of probability, based on confidence interval and other testing of key pharmacokinetic parameters, that the majority of patients will experience no meaningful shift in the rate or extent of drug absorption following a switch from the trade name drug.

There are several issues and concerns relevant to switching between formulations of psychotropic medications in at-risk populations. Of particular concern is the potential fragility of patients with schizophrenia, who might not be able to self-monitor their clinical course and side effects. Moreover, dosage titration is considered particularly critical, requiring slow adjustment and, for many patients, serum drug concentration monitoring. Lastly, there are psychological issues concerning the potentially adverse reaction of patients to, for example, the altered appearance of the drug, if they receive no warning about imminent changes in therapy, e.g., automatic pharmacy substitution of the least expensive generic drug for the brand drug.

As outlined in Dr. Marvin Meyer's article,[2] the FDA has issued requirements for the in vitro and in vivo studies necessary for a generic manufacturer to receive an AB bioequivalence rating, e.g., to have the branded and generic drugs considered interchangeable. For many drugs, these pharmacokinetic studies are performed in healthy volunteers. The goal for any clinical study submitted to the FDA is to determine relevant bioavailability parameters, including the area under the plasma concentration versus time curve (AUC) and the maximum concentration observed during the timed interval sampling of the drug (C_{max}), and analyze these data in a specific, predefined fashion. Bioequivalence must be demonstrated for the population and statistical tests performed that model individual variability during the switch in formulations, e.g., individual bioequivalence. The specific criteria employed for bioequivalence approval by the FDA have evolved over time and can be different for certain classes of medications or treatment conditions.

For clozapine, a general waiver was granted by the FDA to allow potential manufacturers of the generic product to perform bioequivalence testing of the generic product at the lowest dosage strength manufactured (in fact, only 1/2 of a 25-mg tablet) in healthy volunteers rather than at the highest dosage strength manufactured, since higher doses of clozapine have been associated with severe adverse events in healthy populations.[3] Moreover, single-dose studies were conducted rather than studies with repeated dosing of the test products to steady-state conditions. Although the waiver allowed for a more conservative method of bioequivalence testing, using patients dosed to steady state in a randomized crossover paradigm, only one of the generic manufacturers (Creighton) chose

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this more difficult but more reliable approach. The waiver further stipulated that in vitro dissolution testing be performed between the test and branded product and that those products should be considered similar by a priori criteria. As described in the article by Dr. Y. W. Francis Lam and colleagues,[4] apparently in vitro criteria for dissolution were not met for the comparison of the Zenith Goldline pharmaceutical's product and the currently marketed formulation of Clozaril. Also, the ratio of binders, excipients, and fillers to active drug is not the same for the 25-mg and 100-mg Zenith Goldline tablets, making further extrapolation from the low-dose studies difficult. Therefore, part of the uncertainty regarding clozapine generic substitution is the need to extrapolate data from very low single doses in healthy volunteers and apply those data to traditional doses with multiple 100-mg tablets at steady state in patients requiring this medication. Dr. Neal Cutler[5] reviewed the issues surrounding the use of healthy volunteers versus patients in bioequivalence studies of antipsychotics and recommended that these studies be performed in the target population.

Although the FDA waiver for testing of generic clozapine products is of some concern, if there were no clinical changes or patient pharmacokinetic data showing differences subsequent to a switch in formulations, then this issue would be of only theoretical interest. However, in an at-risk forensic population with persistent psychotic disorders, Dr. John Kluznik et al.[6] found an alarmingly high rate of clinical worsening and overt relapse. On the basis of their analysis, the potential cost savings of the generic product are offset by the increased costs associated with this population's destabilization. These results can, in part, be explained by the preliminary pharmacokinetic results of a randomized crossover bioavailability study presented by Dr. Lam and colleagues.[4] There was a clear tendency for the serum drug concentrations of Zenith Goldline–treated patients to be numerically lower than those achieved in the same patients at steady-state on Clozaril treatment. The most notable difference observed was in the rate of absorption, as measured by C_{max}. It has been suggested by Kapur and colleagues[7] that reduced maximal concentrations of an antipsychotic that is loosely bound to dopamine D_2 receptors could negatively influence efficacy. The study by Dr. Ereshefsky and colleagues[8] (preliminary report by Lam et al.[4] is included in this supplement) was not designed as a classical bioequivalence trial. Instead, it was naturalistic, allowing enrollment of long-term clozapine-treated outpatients as well as stable inpatients. The usual restrictions on comorbid medical illness, ideal body weight limits, and concomitant drugs were not employed, provided that the status of the patient remained fairly constant.

Given the financial and clinical stakes involved, it is not surprising that clozapine bioequivalence has become controversial. According to a recent report, close to 22,000 patients are on treatment with the Mylan Pharmaceuticals brand of clozapine, and adverse events have been reported in only 20 patients.[9] In addition, Zenith Goldline Pharmaceuticals reports that 21,000 patients have been "successfully" switched from Clozaril to their generic clozapine.[10] The sensitivity of their database for clinical sequelae is limited by the unknown response rate of the treating clinician in documenting clinical response in a national registry. At the North Carolina Department of Health and Human Services, Division of Mental Health, Developmental Disabilities, and Substance Abuse Services, the switch from Clozaril to Zenith Goldline generic clozapine was undertaken at their 4 psychiatric hospitals after substantial planning and discussion regarding the transition.[11] Serum clozapine concentrations were obtained before and after the switch in selected patients. No difficulties were reported subsequent to the switch, nor were trough levels significantly different. However, at 1 of the hospitals, the formulary committee noted that many of the clozapine levels were well above the usual therapeutic range of 350 ng/mL. In 16 instances, the levels were > 400 ng/mL (written communication, Robert J. Allen, M.S.Pharm., B.C.P.P., Pharmaceutical Services, North Carolina Department of Health and Human Services, March 14, 2000), raising sensitivity issues in detecting a difference, since reductions in concentrations may matter only if the levels drop below a certain threshold. Additionally, Lam and colleagues'[4] preliminary report also demonstrates similar trough concentrations between formulations, despite their observations for significantly slower absorption rate and C_{max} for the Zenith Goldline formulation.

At the Texas Department of Mental Health and Mental Retardation, the standing policy is to use generically equivalent products whenever possible.[12] However, the policy does recognize that

> some situations exist where FDA-required studies have shown no statistical difference between generic and the brand name product, but potential differences may exist in individual patients. . . . Although not studied, this potential for such differences may exist when patients are switched from one manufacturer's generic clozapine product to a different manufacturer's generic product.

Therefore, the Texas Department of Mental Health and Mental Retardation policy advises that for patients newly started on clozapine treatment, the generic should be used. Patients who are stabilized on treatment with clozapine, whether it is the generic or branded formulation, should not be switched to a different manufacturer's product unless it can be done under close supervision and with consent. This supervision should include monitoring of serum clozapine levels. If the switch is performed with an outpatient, then the availability of clozapine levels and extremely frequent patient evaluations are recommended.

So how does the clinician or health system proceed in managing both potential patient risk and cost savings? For a patient just starting clozapine treatment, any marketed formulation can be safely and effectively started on an individual basis. The FDA terms this *prescribability*, and it is reasonable to consider a single-source generic drug as a cost-based alternative for new patients or those restarted on the medication after a significant intervening interval. However, in patients currently stabilized on and benefiting from Clozaril therapy, a clinical assessment of the benefits and risks to the patient should precede the cost-benefit analysis. It is also prudent to discuss strategies to manage possible risk (irrespective of how unlikely) with the patient and caregiver, including more frequent monitoring and serum clozapine concentration monitoring, as appropriate. Additionally, one should remember that generic-to-generic formulation switches are not evaluated by the FDA. For example, a switch from one generic formulation of clozapine to another might be associated with larger-than-anticipated shifts in both the rate and extent of absorption. Further study is needed to address several dimensions of the posited issues, not only specific to clozapine, but also the larger health-policy–related procedures for generic testing, approval, and postmarket monitoring.

Specifically, further studies of the interchangeability of generic and branded clozapine should include the following features:

- The use of patients (inpatients or outpatients) instead of healthy volunteers as the subject sample
- The use of 100-mg tablets and 25-mg tablets and doses within the manufacturer's recommended range
- A sufficient number of subjects to ensure statistical power
- Pharmacokinetic and clinical response outcome measurements
- Frequent monitoring, for example, weekly for the first month then every 2 weeks or once a month for the duration of the study (6 months)
- Long-term follow-up

However, until further studies comparing the branded and generic formulations of clozapine are conducted, procedures must be established for switching patients from Clozaril to generic clozapine (Table 1). Each institution or health care system should create a protocol for educating patients, their families, and staff about the switch. Patients should be monitored for signs of clinical worsening or tolerance problems. In addition, these procedures should include monitoring blood clozapine levels at weeks 1, 2, and 4 after such a switch in both inpatients and outpatients. To prevent any confusion or potentially serious psychological adverse effects in patients, an institution's pharmacy should avoid a switch in formulation without informing the staff.

Table 1. Recommendations for Switching Patients From Clozaril to Generic Clozapine

Educate patients, their families, and staff
Monitor patients for signs of clinical worsening or tolerance problems
Monitor switched patients' blood clozapine levels at weeks 1, 2, and 4 after the switch
Monitor blood clozapine levels as frequently in outpatients as in inpatients
Inform the staff about any changes in the pharmacy or dispensary; do not make changes without informing the staff

In February 2001, the FDA recommended that Zenith Goldline Pharmaceuticals conduct a new bioequivalence study of its generic clozapine product.[13] Such a study is crucial if we are to be assured that these products are interchangeable. We eagerly await the results of such a study. Meanwhile, we continue to recommend caution in switching patients from Clozaril to generic clozapine (see Table 1).

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