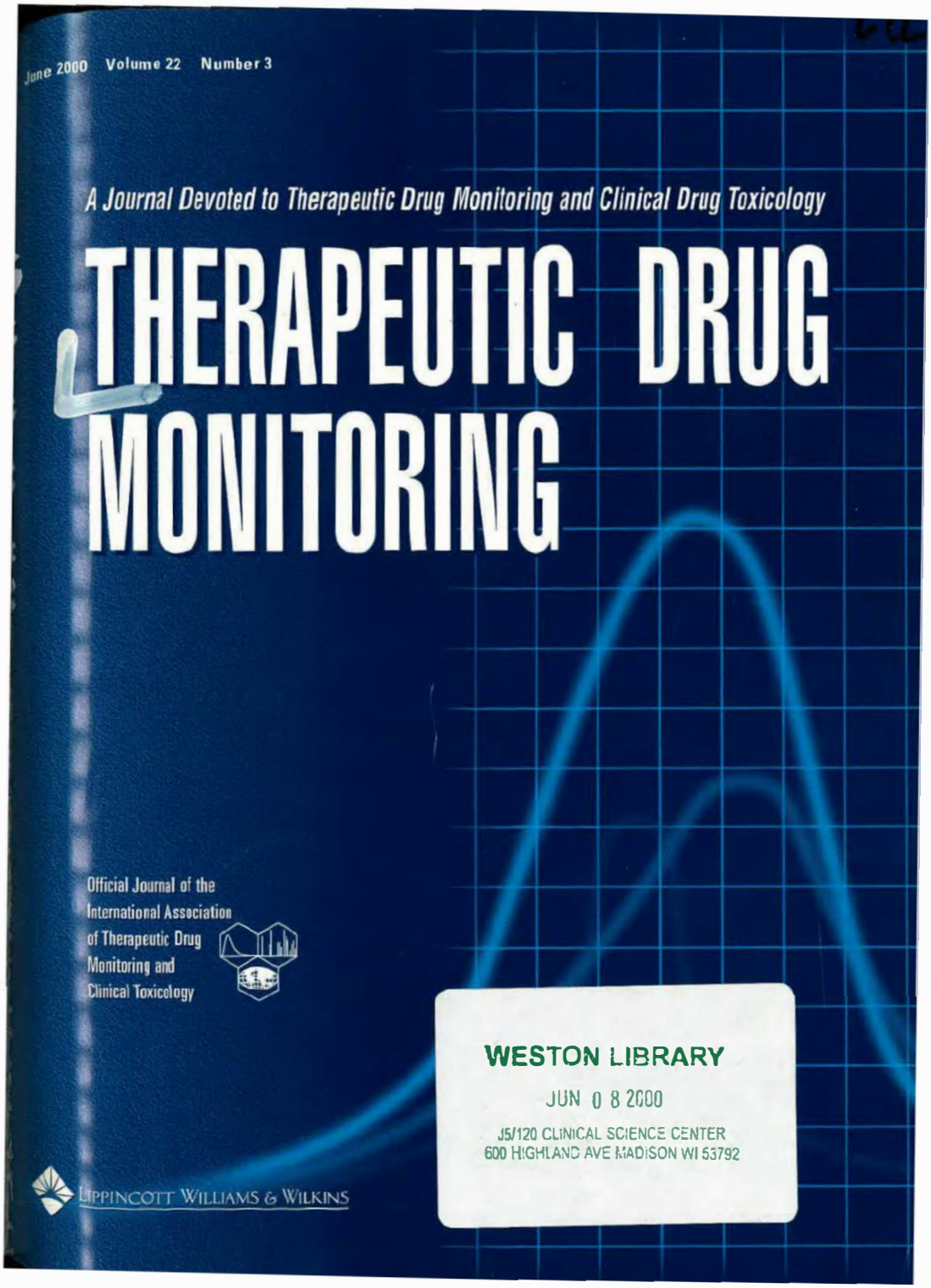

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Recommendations for Bioequivalence Testing of Cyclosporine Generics Revisited

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Summary: The immunosuppressant cyclosporine is generally considered a critical-dose drug. The validity of standard criteria to establish bioequivalence between cyclosporine formulations has recently been challenged. Recommendations included establishment of individual bioequivalence rather than average bioequivalence, establishment of bioequivalence in transplant patients and in subgroups known to be poor absorbers, as well as long-term efficacy and safety studies in transplant patients. However, at the moment individual bioequivalence is a theoretical concept, the practical benefits of which have not statistically been proven. The proposed patient pharmacodynamic studies can be expected to require an unrealistically high number of subjects to achieve sufficient statistical power. It is well established that the common practice of blood-concentration–guided dosing of cyclosporine efficiently compensates for interindividual and intraindividual variability and allows for safely switching cyclosporine formulations as bioinequivalent as Sandimmune and Neoral. Recent studies comparing the generic cyclosporine formulation SangCya with Neoral, including individual bioequivalence, bioequivalence in transplant patients, and long-term safety after switching from Sandimmune to SangCya, confirmed that it was valid to conclude bioequivalence of both cyclosporine formulations based on standard average bioequivalence criteria. Present FDA guidelines for approving bioequivalence can be considered adequate and sufficient for generic cyclosporine formulations. **Key Words:** Cyclosporine—Cyclosporine generics—Bioequivalence—Individual bioequivalence—Therapeutic drug monitoring.

Mostly as a result of the introduction of the undecapeptide cyclosporine as immunosuppressant, graft and patient survival have significantly improved during the last two decades and transplantation is an established standard procedure at most large medical centers. However, there are considerable costs for immunosuppressive therapy requiring life-long maintenance to prevent the transplant organ from being rejected (1,2). In the United States and Europe there are more than 200,000 transplant recipients requiring daily immunosuppressive therapy for the rest of their lives, the majority of whom are receiving immunosuppressive drug regimens based on cyclosporine. Worldwide sales of the innovator's cyclosporine formulations Sandimmune and Neoral (Novartis Pharma, Basel, Switzerland) were estimated at US$ 1.3 billion in 1997. In the United States, the innovator's patent protection expires after 17–20 years and other companies are then free to manufacture interchangeable generic products. Novartis' composition of matter patent on cyclosporine expired in the United States in September 1995. One generic cyclosporine formulation, SangCya (SangStat Medical, San Mateo, CA, USA), has recently been approved by the United States Food and Drug Administration (FDA). Others have filed for approval.

In 1984, the Drug Price Competition and Term Restoration Act (3) allowed the FDA to use a simplified approval process for generic drug products, the so-called

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abbreviated new drug application (ANDA) (4). The FDA's approval process of generic drugs evaluates chemistry, manufacturing and controls, in vivo bioequivalence, labeling, in vitro dissolution if applicable, and includes inspection and auditing of all facilities (5). Because the efficacy and safety of an innovator's drug has already been established, the FDA regulations are promulgated based on the belief that there is no reason to repeat the same studies with the generic version of the drug that contains exactly the same molecular entity as the innovator's product. Because of the lower costs of development and competition in the market, generic drugs usually sell for significantly less than the price of the innovator's product before the availability of generics. It is generally agreed that the prescribing and use of generic drugs lead to considerably reduced cost. Generic drugs also have the potential to improve the quality of care. Lower-cost alternatives may improve adherence to therapies for patients who cannot afford innovator drugs, and these alternatives provide an increased duration of therapy for patients with capped medical benefits. During the last 27 years, the FDA has approved more than 5,000 generic drugs for marketing in the United States (5). To date, the FDA is not aware of any validated study of an FDA-designated equivalent generic product that met FDA specifications but that was not equivalent to the corresponding innovator's product (6,7). In addition, the FDA's investigation of single cases of decreased efficacy or increased toxicity never revealed problems attributed to substitution of one approved product for another therapeutically equivalent product (7). In spite of this excellent safety record, there is a great reluctance by many clinicians to use generic equivalents for so-called "critical-dose drugs." Although there is no official definition for "critical-dose" or "narrow-therapeutic-index" drugs, and no general consensus as to which drugs fall within this category (8), bioequivalence-related issues of critical-dose drugs have been discussed intensively. Benet and Goyan (9) defined narrow-therapeutic-index drugs as "those for which small changes in pharmacokinetic response lead to marked changes in pharmacodynamic response." Accordingly, cyclosporine is generally regarded as a typical critical-dose drug (10–15). Bioequivalence testing procedures, especially in the case of critical-dose drugs, have been criticized in the past for many reasons, most of which potentially apply to cyclosporin (9,10,12,13). A fundamental problem is the definition of bioequivalence, which is based on the assumption that bioavailability (rate and extent) is a valid surrogate for efficacy and safety (16,17). This requires a clinically significant association between blood/plasma concentrations and pharmacodynamic effects that is not necessarily always the case. However, for cyclosporine the relationship between pharmacokinetics and safety has been extensively studied and provides the basis for the generally accepted blood-level–guided dosing regimens. Several other potential issues regarding the interchangeability of cyclosporine formulations are of concern to clinicians. There is doubt that the results of pivotal bioequivalence studies that are conducted in healthy volunteers are extrapolatable to transplant patients who exhibit several factors affecting cyclosporine pharmacokinetics that are not present in healthy volunteers (see below and Fig. 1). This applies especially for subpopulations of patients who are known poor absorbers. Intraindividual variability of cyclosporine is a critical clinical issue that has been associated with acute and chronic rejection (18,19) and cannot be addressed by pivotal healthy volunteer trials. This translates into suspicion that standard bioequivalence testing may not be a valid approach to establishing long-term safety and efficacy in transplant patients.

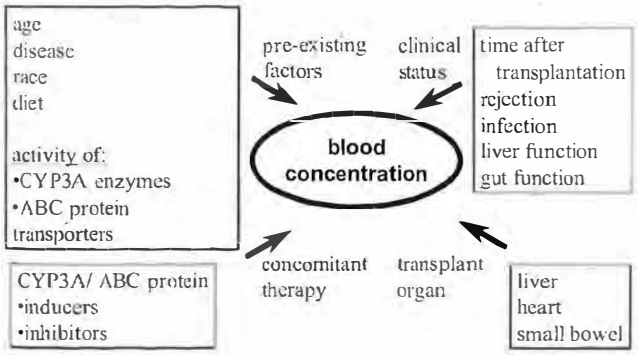

FIG. 1. Factors potentially affecting cyclosporine pharmacokinetics in transplant patients.

TABLE 1. *Comparison of guidelines and recommendations to establish bioequivalence and to switch between cyclosporine formulations*

Recommendation	Johnston et al., 1997[10]	Sabatini et al., 1999[13]	Kahan, 1999[14,21]
Average/individual bioequivalence	Validity of average bioequivalence questionable	Demonstration of individual bioequivalence should be mandatory for FDA approval	Average bioequivalence is a valid approach to establish interchangeability, individual bioequivalence should be demonstrated for the first CsA generic approved
Bioequivalence studies in patients after transplantation	Should be required for all CsA generics	Should be required for FDA approval of all CsA generics	Recommended for first CsA generic approved
Bioequivalence studies in subpopulations that are poor absorbers	Should be required for all CsA generics	Should be required for FDA approval of all CsA generics	Recommended for first CsA generic approved
Long-term efficacy and safety studies in transplant patients	Should be required (study period >3 months)	Not addressed	6-months pre-marketing follow-up
Physicians and patients must approve switch of CsA formulations even if bioequivalent	Not addressed	Yes	Not required

CsA, cyclosporine.

The question has been raised by several authors (10, 12,14,20) as to what extent the standard bioequivalence criteria used by the FDA and most drug agencies in other countries address these concerns and the sufficiency of these criteria to establish the safety of substituting cyclosporine formulations. This has also been discussed in recent meetings (13,21*). This has resulted in several different and sometimes contradictory guidelines and recommendations (Table 1). It was our goal to critically review cyclosporine bioequivalence issues and the discussed recommendations in light of bioequivalence and clinical data that is presently available for several generic cyclosporine formulations and in light of the extensive experience with switching transplant patients between the innovator's bioequivalent cyclosporine formulations as well as between the bioinequivalent Sandimmune and Neoral formulations.

CYCLOSPORINE FORMULATIONS

Recognizing the limitations of the original cyclosporine formulation Sandimmune, a crude oil-in-water droplet mixture (22), the innovator (Novartis Pharma, Basel, Switzerland) developed a microemulsion preconcentrate, Neoral, that improved emulsification and dispersion of cyclosporine in the small intestine and resulted in better and more reproducible absorption (23,25). From the beginning, Neoral was developed to increase cyclosporine bioavailability and, therefore, to be bioinequivalent (i.e., suprabioavailable) to Sandimmune (10,20,24). In fact, Sandimmune and Neoral should be considered different drug products (20).

In healthy volunteer studies (25,26) as well as in clinical studies in transplant patients (23–25,27) and psoriasis patients (28,29), Neoral cyclosporine pharmacokinetics differed from those of Sandimmune, yielding increased maximum blood concentration (C_{max}), decreased time to reach C_{max} (t_{max}), and increased area-under-the-time–concentration curve (AUC) (23). Depending on the dose, the relative bioavailability of Neoral in healthy volunteers was 1.7-fold to 2.4-fold and the C_{max} 1.9-fold to 2.1-fold higher than after the same Sandimmune cyclosporine dose (26). In de novo recipients of kidney transplants, depending on the time after transplantation, dose-normalized AUCs were 32–63% higher than in Sandimmune-treated patients (27). The mean increases of AUC and C_{max} of 39% and 15%, respectively, in stable recipients of kidney transplants after switching from Sandimmune to Neoral (30) were smaller than in the healthy volunteer studies (26). Although based on healthy volunteer studies, a conversion factor of 0.6 (Neoral:Sandimmune) was estimated, transplant patients were switched 1:1(25). In a clinical study in 55 stable recipients of kidney transplant, switching from Sandimmune to Neoral on a 1:1 basis resulted in 22% higher cyclosporine trough blood concentrations (31). However, patients with higher cyclosporine doses before conversion from Sandimmune to Neoral are more likely to require dose reduction in the postconversion course. When switched from Sandimmune to Neoral, good absorbers remain good absorbers whereas poor absorbers become good absorbers (32). The higher bioavailability and different

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pharmacokinetic pattern of Neoral raised several safety concerns that required clarification in clinical studies (23–25). The high cyclosporine C_{max} after Neoral was of special concern because high cyclosporine C_{max} values have been related to short-term renal vasoconstriction and possibly chronic cyclosporine nephropathy (33). Another concern was the higher total exposure of patients during conversion from Sandimmune to Neoral (23). The conversion protocol recommends starting Neoral at the preconversion dose (1:1 conversion) with subsequent dose adjustments according to cyclosporine trough blood concentrations. It was necessary to assume that the greater exposure to cyclosporine from the microemulsion formulation might increase the nephrotoxic risk. In fact, adverse events such as hypertension, nephrotoxicity, and acute rejection have been reported after conversion (30). However, as of today, despite the two products' significant pharmacokinetic differences, clinical studies have established a safety and tolerability profile of Neoral comparable to that of Sandimmune (24). Long-term studies did not show any statistically significant differences between recipients of kidney transplants treated with Sandimmune and those treated with Neoral in terms of safety, including creatinine concentrations, patient and graft survival, as well as the incidence of acute rejection (23,24,27,34,35). This is not surprising: because of the drug's highly intraindividually and interindividually variable pharmacokinetics and narrow therapeutic index, cyclosporine doses must be adjusted according to cyclosporine blood concentrations (36). Regular therapeutic drug monitoring is required, and the cyclosporine concentrations are kept in a narrow target concentration range that is independent of the cyclosporine formulation. However, because of its improved dose linearity and lower intraindividual pharmacokinetic variability, Neoral is generally considered to have proven benefits to patient care over Sandimmune (2,10,24,27).

In October 1998, the FDA approved SangCya (Sangstat Medical, Menlo Park, CA, USA) as the first generic cyclosporine formulation in the United States. SangCya is a nano-dispersion formulation based upon Sangstat's CPLF formulation technology (37). Bioequivalence with Neoral was not only established in pivotal healthy volunteer studies (38), but also in recipients of kidney and liver transplants (39,40) (Table 2, Fig. 2). In addition, individual bioequivalence between SangCya and Neoral was demonstrated (41) (Table 3, see below) following the draft FDA procedures (11,42). Safety and efficacy of SangCya was established in patients with kidney grafts during a 9-month observation period (43).

Healthy volunteer studies demonstrating bioequivalence with Neoral (Table 2) have been published for two other generic cyclosporine formulations, Neoplanta (Hanmi Pharmaceutical, Seoul, Korea) (44,45) and Cipol-NR (Chong Kun Dang, Seoul, Korea) (46). Like Neoral, both are microemulsion formulations (46,47). The difference between Neoplanta and Neoral is that Neoplanta uses dimethyl isosorbide instead of ethanol as the solvent (48). In de novo recipients of renal transplants, Neoplanta and Neoral (n = 20 for each group) showed similar efficacy in preventing graft rejection and similar tolerability (48).

VARIABILITY OF CYCLOSPORINE PHARMACOKINETICS

The significantly lower pharmacokinetic variability of cyclosporine after administration of Neoral compared to Sandimmune is commonly regarded as the major im-

TABLE 2. *Comparison of the results of bioequivalence studies in healthy volunteers and patients who have had a transplantation with cyclosporine formulations (test) bioequivalent to Neoral (reference)**

Cyclosporine	Subjects	n	C_{max} ratio (%) Point Estimate	C_{max} ratio (%) 90% CI	AUC ratio (%) Point Estimate	AUC ratio (%) 90% CI	Ref.
Test Formulation							
SangCya	Fasted male healthy volunteers	36	99	97–104	99	97–103	38
SangCya†	Fasted male and female healthy volunteers	20	95	90–101	97	92–102	41
SangCya	Fasted/fed male healthy volunteers	24	97	91–104	100	96–105	38
SandCya	Fasted female healthy volunteers	28	92	87–100	95	92–102	38
SangCya	Fasted male African-American volunteers	10	96	81–108	90	83–96	38
Neoplanta	Fasted male Korean healthy volunteers	24	97	90–101	99	94–102	45
Cipol-N	Fasted male Korean healthy volunteers	24	103	100–106	100	96–104	46
SangCya	Kidney transplant patients	32	90	84–102	94	86–106	39
SangCya	Liver transplant patients	26	86	81–106	95	89–109	40

* The AUC ratio in healthy volunteer studies is based upon the $AUC_{0-\infty}$, the AUC ratio studies on the $AUC_{0-\tau}$ in patients after transplant. Neoplanta[45] and Cipol-N[46], like Neoral[22], are microemulsion cyclosporine formulations, whereas SangCya is a nano-dispersion formulation based upon Sangstat's CPLF formulation technology[37].

† Analysis of individual bioequivalence see Table 3.

CI, confidence interval.

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