REVIEW

# Generic cyclosporine formulations: more open questions than answers

Dario Cattaneo,[1,2] Norberto Perico[1,2] and Giuseppe Remuzzi[1,2]

1 Department of Medicine and Transplantation, Ospedali Riuniti di Bergamo, Mario Negri Institute for Pharmacological Research, Bergamo, Italy
2 Center for Research on Organ Transplantation, ''Chiara Cucchi De Alessandri & Gilberto Crespi'' Mario Negri Institute for Pharmacological Research, Ranica, Bergamo, Italy

**Summary**

The introduction of cyclosporine (CsA) in clinical practice has significantly improved patient and allograft survival after organ transplantation. The new microemulsion CsA formulation, Neoral, has been associated with a more reproducible absorption and a better patient outcome as compared to the old formulation Sandimmune. Recently, several generic CsA formulations have been tested as bioequivalent to Neoral. Bioequivalence tests have been performed in selected groups of young, healthy male volunteers usually in single-dose studies, and then extended to completely different population, such as transplant recipients. However, growing body of evidence shows that CsA pharmacokinetics in healthy subjects is different from that of transplant patients, treated chronically with CsA. Therefore, converting patients from Neoral to the new generic formulations could be detrimental, exposing patients to increased risk of graft function deterioration and graft loss. Thus, more research and more accurate bioequivalence tests are required to address the unanswered problems dealing with the generic CsA formulations.

## Introduction

Cyclosporine (CsA), one of the principal immunosuppressants currently used to prevent graft rejection, has largely contributed to improve patient and allograft survival [1].

CsA is characterized by a narrow therapeutic index, significant side effects, and a strong correlation between CsA exposure and clinical outcome. To this, major efforts have been devoted to individualize CsA dosing based on pharmacokinetic parameters, in order to minimize the toxicity and improve the risk-to-benefit ratio [2].

Despite more than 20 years of its clinical use, one of the challenge in CsA management is the poor, variable and unpredictable absorption, associated with a great intra- and inter-patient variability. This is a key factor, since the greater the day-to-day variability in CsA exposure, the higher the risk of acute rejection in organ transplant recipients [3]. It has been also shown that high intra-individual variability of CsA exposure enhances chronic rejection incidence, and eventually health care costs [4]. These observations underline the role of the pharmaceutical formulation and related factors to clinical outcome. The excipients used in a drug formulation are, by definition, inactive and play no role in the pharmacological action of the drug. However, early [5,6] it was realized that the nature of the excipients used, and changes in the way oral drug preparations were formulated could have very great effects on the amount of drug absorbed. In addition, some excipients are known to modify the activity of the multidrug resistance proteins (MDR1), an efflux pump which removes lipophilic drugs from the intracellular space, and/or metabolic enzymes like cytochrome P450 subclass 3A4 [7]. Thus, the variable oral CsA bioavailability represents a biopharmaceutical risk factor and deserves particular attention when new formulations are used.

## Limits of the CsA Sandimmune formulation

Sandimmune (Novartis, Basel, Switzerland), an oil-based suspension of CsA immiscible with water, was first used

in preclinical studies in 1977 and thereafter, introduced in clinical practice in 1984 [8].

The bioavailability of Sandimmune is extremely variable, ranging from 5% to 50%. This formulation is characterized by intra-individual erratic oral absorption, greatly influenced by bile flow, the composition of biliary, pancreatic, and duodenal/small bowel secretion, the function and motility of the small bowel, and food [9,10].

The excipients may also play a significant role, influencing the pharmacokinetic properties of Sandimmune. Recently, it has been shown that Sandimmune capsules, where the drug is dissolved in olive oil in a soft gelatin capsule, and Sandimmune solution, where the drug is dissolved in corn oil, were not bioequivalent in a subset of poor absorbers [11]. Indeed, it should be taken into account that inter-individual variation in the Sandimmune absorption has been also reported, which segregates three distinct populations of patients, defined as 'low', 'intermediate', and 'high' absorbers [12].

To overcome these limitations, therapeutic drug monitoring and adjusting CsA Sandimmune dose to individual need of CsA trough blood levels ($C_0$) has widely adopted. However, with this CsA formulation, the pharmacokinetic approach is not of universal help, as documented by findings that some patients experience acute graft rejection even in the presence of adequate or high blood CsA concentration, while others develop toxicity at CsA trough level below normal [13].

The variations in CsA absorption profile with Sandimmune led to efforts in developing a new CsA formulation.

## The novel CsA Neoral formulation

The new formulation, CsA Neoral (Novartis, Basel, Switzerland), was based on a microemulsion that in the gut disperses more rapidly, leading to increased and more reproducible absorption profile compared with the old formulation. As a consequence, a closer pharmacokinetic relationship between CsA trough concentration and area under the time–concentration curve ($AUC_{0-12}$) [14,15] was reported. These findings renewed the interest for the application of CsA therapeutic drug monitoring.

The favorable kinetic profile of Neoral compared to the conventional formulation was confirmed in the early phase post-transplant [16] as well as in stable renal transplant recipients [17]. Although safety and tolerability of the two formulations were comparable, the incidence of acute rejection was lower in the Neoral group. In patients previously treated with Sandimmune, the conversion to Neoral was associated with an increase in the CsA exposure. Of note, 20% of patients categorized as 'low' absorbers while on traditional formulation, became 'intermediate' or 'high' absorbers as early as 15 days after conversion to Neoral (Fig. 1), further supporting the beneficial pharmacokinetic effect of the new formulation.

The advent of Neoral, with its peculiar kinetic profile, has also provided new opportunities to explore more sensitive and feasible CsA monitoring strategies as surrogate markers of drug exposure in transplant patients. Several single- or limited-sampling point tools have been developed so far for patients on Neoral-based immunosuppression [18]. On this line, recent evidence in liver and kidney transplant recipients indicate that 2-h postdose point sampling ($C_2$) is a sensitive tool for fine-tuning CsA dosage [19,20] when Neoral formulation is used.

The more reproducible absorption and blood CsA concentrations achieved with Neoral are likely to result in the reduction in the incidence of acute rejection episodes in the early period as well as in the stable transplant recipients [21].

Overall, these observations further underline the impact of the pharmaceutical formulation on patient monitoring and clinical outcome and support the superiority of the
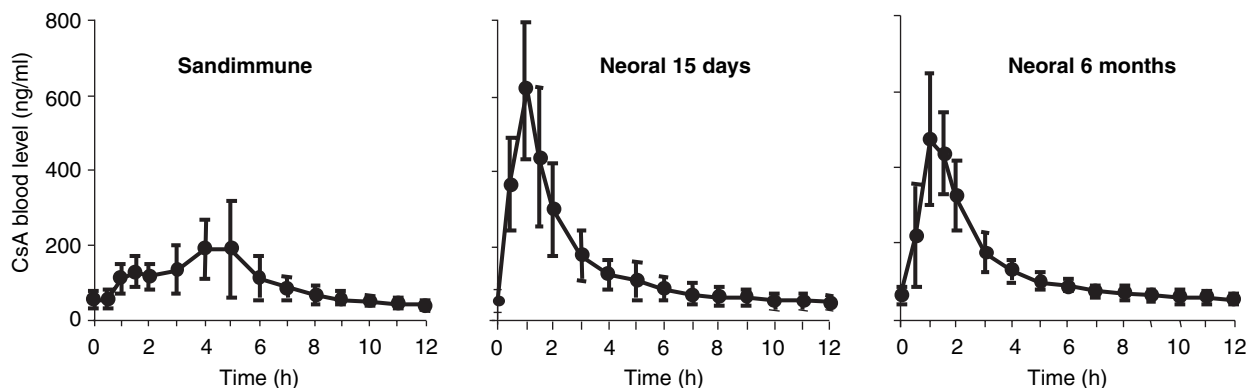


**Figure 1** CsA blood concentration in 'low' absorber patients before (Sandimmune) and after conversion to Neoral formulation (day 15 and month 6) (modified from [17]).

CsA Neoral over the traditional Sandimmune formulation.

## The advent of novel CsA generic formulations

In clinics the use of generic products is widespread and now plays an important role in the available therapeutic armamentarium. This also applies to transplant medicine. Several drugs which represent cornerstone in the therapeutic management of transplant patients currently have generic alternatives, including those belonging to antihypertensive and immunosuppressant classes.

Because the efficacy and safety of an 'innovator' drug has already been established, the regulatory agencies for drug approval, like CPMP (Committee for Proprietary Medicinal Products for bioequivalence testing in Europe for EMEA) and FDA, use simplified approval process for generic drug products [22,23]. Specific requirements are that generic formulations have to contain the same molecular entity and should prove to be bioequivalent with the innovator's product. Theoretically, the generic preparations would improve adherence to treatment for their lower cost in countries with no social insurance. The introduction of generic drugs in routine clinical practice, therefore, would significantly improve the quality of care, or even, allowing access to therapy in patients living in emerging countries where the health resources are already limited. However, are the concepts of generic formulations applicable to all drugs, including those with narrow therapeutic range- or critical dose-drugs, like CsA?

In 1995, Novartis' composition of matter patent on CsA expired. Since then, other companies are free to manufacture interchangeable generic products. Up to now, several generic CsA formulations have been developed [24–31], and most of them have recently become available in Europe. They demonstrate bioequivalence criteria according to the current regulations [32]. Unfortunately, these rules apply indiscriminately to all drugs, independently of whether they belong to narrow therapeutic range and critical dose agents. Actually, the bioequivalence guidelines for approval of generic formulations require a similar average bioavailability compared with the reference formulation, with the 90% confidence interval of the relative mean AUC and $C_{max}$ of the test to reference formulation within 0.8–1.25 [33]. The main limitation of this approach is the subject population currently used to test the bioequivalence criteria. Indeed, most of the comparative studies involve selected groups of young, male, healthy subjects. But, the findings are then extended to completely different population, such as transplant recipients. However, growing body of evidence shows that CsA pharmacokinetics in healthy subjects is different from that of transplant patients.

Moreover, several of the bioequivalence studies consider single CsA dose administration, but this is not the best approach for testing, since CsA absorption varies with time, and the drug formulation may influence the time to reach the steady state [34]. A single-dose pharmacokinetic assay, which is the present requirement for bioequivalence, does not measure variability of drug exposure, $C_{max}$ or $T_{max}$ as the patient progresses towards the steady state. Single-dose bioequivalence also does not capture any metabolic differences that may occur in a transplant patient. Since CsA is characterized by a narrow therapeutic index and serious drug-related toxicity, it is not ethical to expose healthy subjects to repeated, chronic dose of the drug. Therefore, single-dose testing in these subjects is considered sufficient to assess bioequivalence. However, this should be only the starting but not the final step. More pertinent it would be to confirm bioequivalence in organ transplant recipients after repeated drug dosing, when exposure to CsA is stabilized [34]. Differences in the pharmacokinetic pattern according to CsA formulations have been observed in different populations including children [35], and blacks [36]. Also diseases, such as diabetes [37] predispose patients to altered absorption of CsA. In addition, the type of transplanted organ can influence CsA pharmacokinetics [38,39]. Analysis of the fast/fed data [40] from different studies on two generic formulations of CsA shows that each version behaved like Sandimmune and not Neoral. This suggests that the absorption of CsA from these generic formulations are different to Neoral.

Together, these observations argue against the value of testing bioequivalence of different CsA formulations just in healthy volunteers. Therefore, the available evidence cannot be considered conclusive unless 'Clinical' bioequivalence is also tested in transplanted patients. In 2001 two independent panels of transplant and pharmacokinetic experts from Europe [41] and USA [42] convened to address issues associated with approval of generic immunosuppressant equivalents and to formulate consensus statements useful to better test bioequivalence for these drugs. Although both these conferences called to urge action, it should be mentioned that, after three years, none of the proposed guidelines have been applied, and none of the main concerns have been adequately addressed, despite a growing literature in the field of generics. Following is an update of the most recent developments on different CsA formulations published after the consensus guidelines.

An example of the limits of criteria now-a-day used to test generic formulations is given by SangCya (or Sang-35, SangStat Medical Corporation, Fremont, CA, USA), the most extensively studied generic alternative to Neoral. After a series of studies in healthy volunteers, FDA

approved its use in 1998. Three years later FDA announced the voluntary nationwide recall of SangCya oral solution by the manufacturer 'because of clinical evidence that the generic drug's availability is reduced relative to Neoral oral solution in kidney transplant recipients when the drug is administered with apple or orange juice' as recommended in its labeling [43].

Recently, another CsA generic formulation has been approved by FDA. Gengraf (Abbott Laboratories, Abbott Park, IL, USA) is a branded generic to Neoral in capsule form used for the prevention of graft rejection in kidney, liver, and heart transplant recipients [27]. A milligram-for-milligram interchangeability of Gengraf for Neoral has been demonstrated in stable renal transplant recipients [44], as shown by no differences in CsA $C_{max}$ and AUC between the two formulations. In addition Gengraf was well tolerated, with a safety profile comparable to the safety profile of Neoral. Although this product has undergone extensive testing with orange and apple juice, it was suggested that patients should exercise caution when mixing CsA-modified liquid with nontested vehicles [42]. Moreover, data were achieved in stable kidney transplant recipients, which makes difficult to extrapolate them to de novo transplant patients early postsurgery. Similarly, these findings cannot be applied to liver or heart transplantation without formal testing in the specific setting. In the scanty literature available about Gengraf [45], none of the previously raised concerns have been addressed. Therefore, the available evidences are not enough supportive of bioequivalence between Gengraf and Neoral.

In recent report by Lee and colleagues [25], the generic product Neoplanta (Hanmi Pharmaceutical, Ltd, Seoul, Korea), a new CsA microemulsion, was compared with Neoral in 24 healthy male volunteers who received a single dose of the study drug in a cross-over design. The pharmacokinetic parameters fell within the required confidence limits, thus meeting the bioequivalence criteria. However, the statistical analysis indicated both $C_{max}$ and AUC were influenced by the sample assay sequence of the cross-over design [46]. Therefore, there is no evidence that the two formulations may be bioequivalent when administered in organ transplant recipients. Similarly, despite proven bioequivalence in healthy volunteers, no data on clinical bioequivalence have been provided for the new Sigmasporin Microoral (Gulf Pharmaceutical Industries, Julphar, United Arab Emirates) CsA formulation [29]. These concerns should be carefully addressed before Neoplanta and Microoral are introduced in clinical practice.

Consupren (IVAX-CR, Opava, Czech Republic) is an additional generic CsA formulation developed more than 10 years ago in Czec Republic [26]. Similarities in terms of graft outcome and survival between Consupren and Neoral have been reported in kidney and heart transplant recipients [26,47,48]. However, these studies provide a strong example on how generic formulations are usually developed far from the concept of bioequivalence. Indeed Consupren, used at 8 mg/kg dose was considered bioequivalent to Neoral, administered at 3 mg/kg [47]. More important, the $C_{max}$ achieved with Neoral at 2 h postdosing was not reached at the same time point with Consupren [49]. A similar trend has been observed in a cohort of 42 stable kidney transplant recipients converted from Neoral to the new dispersion formulation of CsA, Cicloral (Cicloral, Hexal AG, Holzkirchen, Germany), in a 1:1 dose relation [28,41]. Pharmacokinetic studies performed just before, when patients were on Neoral, and after the switch, when patients were on Cicloral, evidenced a different pattern of correlation between the single time-points ($C_0$, $C_{1.5}$, $C_2$, $C_3$) and the full $AUC_{0-12}$. The latter observations raise another important concern about the generic CsA formulations that unfortunately has not been addressed so far: the management of CsA monitoring. Limited blood sampling strategies (single- or multiple-point) failed with Sandimmune, but succeeded with Neoral, suggesting that these approaches are drug formulation-sensitive. Today, great emphasis is given to the improvement of patient care associated with the CsA $C_2$-based monitoring. If this is true for Neoral, the case of Consupren and cicloral indicate that the same strategy cannot be directly applied to all generic formulations, but *ad hoc* studies need to be planned to address this issue.

All together these examples illustrate the most important open questions related to generic CsA formulations. Nevertheless, one should also consider the additional confounding factor derived from poor- and superabsorbers in a given patient population that will magnify differences in CsA bioavailability between different formulations. These patient subsets must be also considered in bioequivalence testing. Moreover, since the patient pool is not homogeneous, for critical drugs like CsA, close monitoring is required when different formulations are switched each others. Equoral (IVAX-CR, Opava, Czech Republic), is a new formulation tested as bioequivalent to CsA Neoral in 12 healthy volunteers [30] and recently confirmed as clinically bioequivalent in 15 stable renal transplant patients switched from Neoral capsules to Equoral capsules [31]. It should be pointed out, however, that bioequivalence studies should be conducted with a large number of subjects, usually 20–40 [42]. Assuming that no more than 20% of patients treated with Neoral present an atypical CsA absorption profile [12,17], only two to three subjects in each study may have an altered absorption. Since no data have been provided on the variability of CsA levels at each sampling time-point, the results could have been biased, underscoring the impact of poor and/or superabsorbers.

The availability of multiple CsA formulations will also raised concerns about their impact on clinical outcomes. At least two issues should be considered: the use of generics starting immediately after surgery (prescribability), and the switch from the innovator's to the generic product in stable transplant recipients (switchability). The former may have less clinical impact, since the dose of a given formulation could be optimized by monitoring CsA levels starting immediately postsurgery. If differences exist among CsA formulations, they are likely to play a significant role in patients on maintenance therapy. Since proper monitoring of CsA exposure is crucial to optimum immunosuppression, switching between different CsA formulation in patients late after transplant when visit are less frequent, may not provide the same optimal monitoring, with increased risk of graft loss or toxicity. Although a uniform opinion regarding safety of switching among CsA formulations was not reached, clinical recommendations have been proposed in the previous consensus guidelines [41,42]. A switch to a generic CsA formulation should be conducted only under the supervision of the transplant physician, avoiding to mix different CsA formulations, and monitoring CsA blood levels closely during the first week after a change in the formulation, together with frequent monitoring of serum creatinine levels and blood pressure.

One should point out that bioequivalence does not necessarily means clinical equivalence. Inadverted switching between CsA formulations could impact long-term clinical outcomes and graft survival. A recent report following an analysis of the Collaborative Transplant Study database (Opelz G, available at http://www.ctstransplant. org) shows a significantly lower graft survival in renal transplant recipients given a generic CsA formulation as compared with those on Neoral. At one year postsurgery, the overall graft survival for Neoral-treated patients was 88% vs. 78% for generic CsA treated patients. This is only a retrospective analysis that may be biased by several confounding factors, however, it deserves attention. Different studies have shown that the variability of CsA exposure significantly affects short- and long-term graft survival [3,4,50–54], a concept verified using both the traditional CsA $C_0$-based [4,51,53] and the new $C_2$-based [50,52,54] sampling strategy to monitor CsA levels. Therefore, differences in CsA pharmacokinetic parameters, as it might happen between Neoral and generic CsA formulations, may significantly affect the clinical outcome.

## Conclusions

In general, we are fully supportive of the use of generic drugs in clinical practice. Certainly, this strategy will help to increase access to essential medicine, particularly in emerging countries, that have limited resources to afford the cost of innovator products [55]. However, not all generic drugs may need similar requirements for testing bioequivalence versus innovators before entering in the clinical practice. Indeed, the actual bioequivalence guidelines should be applied only for drugs characterized by a wide, well-known therapeutic index, such as antihypertensive, lipid-lowering, non-steroidal anti-inflammatory agents. Usually these drugs are administered at a fixed dose, because difference between the optimal and toxic dose is extremely high. Thus, in such instance, small variation in the pharmacokinetic profile, as it might happen using generics, does not affect the pharmacological and toxicological properties and eventually clinical outcome. Unfortunately, the above mentioned rules apply indiscriminately to all drugs independently of whether they belong or not to narrow therapeutic range and critical dose agents. However, for drugs with narrow therapeutic index, such as CsA, small variation in the pharmacokinetic property of generic formulation may result in a great impact on clinical outcome. This implies that more restrictive criteria are required to test generic formulation of narrow therapeutic index drugs. Three years ago a panel of experts proposed to perform additional studies in which the innovator and the test product should be given in replicate administration in four period crossover [42]. This approach may allow the calculation of both the inter- and intra-patient variability of the two CsA formulations tested. Unfortunately, to our knowledge, this strategy has never been pursued.

Thus, before generic forms of CsA enter into clinical practice, they should be evaluated not only in single-dose healthy volunteers, as mostly it now occurs, but also in chronically treated, heterogeneous populations of transplant recipients to confirm clinical bioequivalence.

Actually, there is a significant lack of articles published in peer-reviewed journals for generic formulations of CsA (Table 1). Transplant clinicians and their patients expect

**Table 1.** Number of publications in peer-reviewed journals on results from studies of Sandimmune, Neoral and other CsA generic formulations.

| CsA | Publication |
| --- | --- |
| Sandimmune | 1218 |
| Neora | 1672 |
| SangCy | 13 |
| Consupre | 25 |
| Neoplant | 3 |
| Gengra | 3 |
| Cicloral | 3 |
| Eo | 1 |
| Equora | 2 |
| Microora | 1 |

information to be available on the efficacy and safety of generic CsA formulations and this should be a priority for future studies.

Experience gained from studies with Sandimmune and Neoral indicates that higher bioavailability of CsA formulation and reduced variability of drug exposure decrease the risk of acute rejection episodes, increase long-term graft survival, and lower treatment costs [4]. Therefore, in the absence of adequate testing prior to federal agency approval, converting patients from the current Neoral to the new generic formulations could be detrimental. Lack of these informations may expose patients to the increased and unacceptable risk of graft function deterioration and graft loss as compared to the traditional Neoral formulation. As a consequence, the apparently lower cost of the generic formulations would be overweighed by the additional costs of further, unscheduled interventions required to monitor patients when graft function rapidly deteriorates. More research is now required to address the still unanswered problems dealing with the generic CsA formulations. Only when these additional information will be available, the time will arrive for the safe place of these drugs as part of the current immunosuppressive regimens in organ transplantation.

## Acknowledgements

## Conflict of interest

## References

1. Hariharan S, Johnson P, Bresnan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Eng J Med* 2000; **342**: 605.

2. Lindholm A, Kahan BE. Influence of cyclosporine pharmacokinetic, trough concentrations, and AUC monitoring on outcome after kidney transplantation. *Clin Pharmacol Ther* 1993; **54**: 205.

3. Savoldi S, Maiorca R, Maderna M, Chiappini R, Corbetta G. Low intrapatient variability of blood cyclosporine levels is correlated with excellent graft survival. *Transplant Proc* 1997; **29**: 288.

4. Kahan BD, Welsh M, Urbauer DL, *et al.* Low intraindividual variability of cyclosporin A exposure reduces chronic rejection incidence and health care costs. *J Am Soc Nephrol* 2000; **11**: 1122.

5. Tyrer JH, Eadie MJ, Sutherland JM, Hooper WD. Outbreak of anticonvulsivant intoxication in an australian city. *Br Med J* 1970; **4**: 271.

6. Holt DW. Digoxin bioavailability. *Lancet* 1978; **2**: 1103.

7. Mountfield RJ, Senepin S, Schleimer M, Walter I, Bittner B. Potential inhibitory effects of formulation ingredients on intestinal cytochrome P450. *Int J Pharm* 2000; **211**: 89.

8. Canadian Multicentre Transplant Study Group. A randomized clinical trial of cyclosporine in cadaveric renal transplantation. *N Eng J Med* 1983; **309**: 809.

9. Holt DW, Mueller EA, Kovarik JM, van Bree JB, Kutz K. The pharmacokinetics of Sandimmun Neoral: a new oral formulation of cyclosporine. *Transplant Proc* 1994; **26**: 2935.

10. Mueller EA, Kovarik JM, van Bree JB, Grevel J, Lucker PW, Kutz K. Influence of a fat reach meal on the pharmacokinetics of a new oral formulation of cyclosporine in a crossover comparison with the market formulation. *Pharm Res* 1994; **11**: 151.

11. Curtis JJ, Barbeito R, Pirsch J, Lewis RM, Van Buren DH, Choudhury S. Differences in bioavailability between oral cyclosporine formulations in maintenance renal transplant patients. *Am J Kidney Dis* 1999; **34**: 869.

12. Keown P, Landsberg D, Halloran P, *et al.* A randomized, prospective multicenter pharmacoepidemiologic study of cyclosporine microemulsion in stable renal graft recipients. *Transplantation* 1996; **62**: 1744.

13. Kahan BD, Grevel J. Optimization of cyclosporine therapy in renal transplantation by a pharmacokinetic strategy. *Transplantation* 1988; **46**: 631.

14. Mueller EA, Kallay Z, Kovarik JM, *et al.* Bile-independent absorption of cyclosporine from a microemulsion formulation in liver transplant patients. *Transplantation* 1995; **60**: 515.

15. Mendez R, Abboud H, Burdick J, *et al.* Reduced intrapatient variability of cyclosporine pharmacokinetics in renal transplant recipients switched from oral Sandimmune to Neoral. *Clin Ther* 1999; **21**: 160.

16. Keown P, Niese D, on behalf of the International Sandimmune Neoral Study Group. Cyclosporine microemulsion increases drug exposure and reduces acute rejection without incremental toxicity in de novo renal transplantation. *Kidney Int* 1998; **54**: 938.

17. Gaspari F, Perico N, Pisoni R, *et al.* How to convert from traditional cyclosporine to the microemulsion formulation in stable renal transplant patients? *Clin Transplant* 1998; **12**: 379.

18. David OJ, Johnston A. Limited sampling strategies for estimating cyclosporin area under the concentration–time

curve: review of current algorithms. *Ther Drug Monit* 2001; **23**: 100.

19. Grant D, Kneteman N, Tchervenkov J, *et al.* Peak cyclosporine levels (Cmax) correlate with freedom from liver graft rejection. *Transplantation* 1999; **67**: 1133.

20. Pescovitz MD, Barbeito R, for the Simulect US01 Study Group, Two-hour post-dose cyclosporine level is a better predictor than trough level of acute rejection of renal allografts. *Clin Transplant* 2002; **16**: 378.

21. Shah MB, Martin JE, Schroeder TJ, First MR. A meta-analysis to assess the safety and tolerability of two formulations of cyclosporine: Sandimmune and Neoral. *Transplant Proc* 1998; **30**: 4048.

22. Commitee for Proprietary Medicinal Products. *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence*. London: CPMP, 2001.

23. Marzo A. Clinical pharmacokinetic registration file for NDA and ANDA procedures. *Pharmacol Res* 1997; **36**: 425.

24. First MR, Alloway R, Schroeder TJ. Development of Sang-35: a cyclosporine formulation bioequivalent to Neoral. *Clin Transplant* 1998; **12**: 518.

25. Lee YJ, Chung SJ, Shim CK. Bioequivalence of Neoplanta capsule to Sandimmune, microemulsion formulations of cyclosporin A in human subjects. *Int J Clin Pharmacol Ther* 1998; **36**: 210.

26. Stephan AG, Barbari A, Masri M, *et al.* A two-year study of the new cyclosporine formulation Consupren in de novo renal transplant patients. *Transplant Proc* 1998; **30**: 3563.

27. Helderman JH, Bennet WM, Cibrik DM, Kaufman DB, Klein A, Takemoto SK. Immunosuppression: practice and trends. *Am J Transplant* 2003; **3** (Suppl 4): 41.

28. Durlik M, Rauch C, Thyroff-Friesinger U, Streu H, Paczek L. Comparison of peak and trough level monitoring of cyclosporine treatment using two modern cyclosporine preparations. *Transplant Proc* 2003; **35**: 1304.

29. Najib NM, Idkaidek N, Adel A, *et al.* Comparison of two cyclosporine formulations in healthy muddle eastern volunteers: bioequivalence of the new sigmasporin microoral and sandimmun neoral. *Eur J Pharm Biopharm* 2003; **55**: 67.

30. Andrysek T, Masri M, Jegorov Z, Veselsky Z, Matha V. Equoral, new cyclosporine drug delivery system, versus neoral: a bioequivalence study in healthy volunteers. *Transplant Proc* 2003; **35**: 207.

31. Masri MA, Haberal M, Rizvi A, *et al.* The pharmacokinetics of equoral versus neoral in stable renal transplant patients: a multinational multicenter study. *Transplant Proc* 2004; **36**: 80.

32. Johnston A, Holt DW. Bioequivalence criteria for cyclosporine. *Transplant Proc* 1999; **31**: 1649.

33. Kahan BD. Considerations concerning generic formulations of immunosuppressive drugs. *Transplant Proc* 1999; **31**: 1635.

34. Kovarik JM, Mueller EA, Richard F, *et al.* Evidence for earlier stabilization of cyclosporine pharmacokinetics in de novo renal transplant patients receiving a microemulsion formulation. *Transplantation* 1996; **62**: 759.

35. Yee GC, McGuire TR, Gmur DJ, Lennon TP, Deeg HJ. Blood cyclosporine pharmacokinetics in patients undergoing marrow transplantation. Influence of age, obesity, and hematocrit. *Transplantation* 1988; **46**: 399.

36. Schroeder TJ, Shah M, Hariharan S, First MR. Increased resources are required in patient with low cyclosporine bioavailability. *Transplant Proc* 1996; **28**: 2151.

37. Chapman JR, O'Connell PJ, Bovington KJ, Allen RD. Reversal of cyclosporine malabsorption in diabetic recipients of simultaneous pancreas and kidney transplant using a microemulsion formulation. *Transplantation* 1996; **61**: 1699.

38. Metha MU, Venkataramanan R, Burckart GJ, *et al.* Effect of bile on cyclosporin absorption in liver transplant patients. *Br J Clin Pharmacol* 1988; **25**: 579.

39. McGuire TR, Yee GC, Emerson S, Gmur DJ, Carlin J. Pharmacodynamic studies of cyclosporine in marrow transplant recipients. A comparison of three assay methods. *Transplantation* 1992; **53**: 1275.

40. Center for Drug Evaluation and Research. *Bioequivalence Review Cyclosporine 100 mg and 25 mg*. Eon Labs Manufacturing Inc, 1999. Review ANDA:#65–017.

41. Pollard S, Nashan BR, Johnston A, *et al.* A pharmacokinetic and clinical review of the potential clinical impact of using different formulations of cyclosporin A. *Clin Ther* 2003; **25**: 1654.

42. Alloway RR, Isaacs R, Lake K, *et al.* Report of the American Society of Transplantation conference on immunosuppressive drugs and the use of generic immunosuppressants. *Am J Transplant* 2003; **3**: 1211.

43. Kovarik JM, Barilla D, MacMahon L, Wang Y, Kisicki J, Schmouder R. Administration diluents differentiate Neoral from a generic cyclosporine oral solution. *Clin Transplant* 2002; **16**: 306.

44. Roza A, Tomlanovich S, Merion R, *et al.* Conversion of stable renal allograft recipients to a bioequivalent cyclosporine formulation. *Transplantation* 2002; **74**: 1013.

45. Carnahan W, Cooper TY. Neoral-to-Gengraf conversion in renal transplant recipients. *Transplant Proc* 2003; **35**: 1308.

46. Lee YJ, Chung S, Shim CK. Decreased oral availability of cyclosporin A at second administration in humans. *Br J Clin Pharmacol* 1997; **44**: 343.

47. Zafar MN, Ahmed E, Alam A, *et al.* Study of a new generic cyclosporine, consupren, in de novo renal transplant recipients. *Transplant Proc* 2002; **34**: 2480.

48. Toman J, Spinarova L, Krejci' J, Hude P, Kopecna E, Kamarad V. Comparison of the efficacy and safety of Consupren solution and Sandimmun Neoral solution, 50 mL in stable heart transplant patients. *Biomed Papers* 2002; **146**: 87.

49. Zafar MN, Abbas K, Naqvi A, Rizvi A. Pharmacokinetics of abbreviated AUC of cyclosporine in renal allograft

recipients in a pakistan population. *Transplant Proc* 1999; **31**: 3304.

50. Chueh SC, Liao CH, Lai MK. Greater variability of dose-corrected cyclosporine C2 concentrations in renal recipients with acute rejection. *Transplant Proc* 2003; **35**: 234.

51. Stoves J, Newstead CG. Variability of cyclosporine exposure and its relevance to chronic nephropathy: a case-control study. *Transplantation* 2002; **74**: 1794.

52. Billaud EM, Antoine C. C2 therapeutic drug monitoring of cyclosporine: source of variability. *Transplant Proc* 2002; **34**: 2828.

53. Waiser J, Slowinski T, Brinker-Paschke A, *et al.* Impact of the variability of cyclosporin A trough levels on long-term renal allograft function. *Nephrol Dial Transplant* 2002; **17**: 1310.

54. Einecke G, Mai I, Fritsche L, *et al.* The value of C2 monitoring in stable renal allograft recipients on maintenance immunosuppression. *Nephrol Dial Transplant* 2004; **19**: 215.

55. Schieppati A, Perico N, Remuzzi G. Preventing end-stage renal disease: the potential impact of screening and intervention in developing countries. *Kidney Int* 2003; **63**: 1948.