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SPECIAL ARTICLE

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Potential clinical implications of substitution of generic cyclosporine formulations for cyclosporine microemulsion (Neoral) in transplant recipients

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Abstract Cyclosporine (CsA) is a critical-dose drug for which a minor change in absorption can have important clinical implications. Generic formulations of CsA are becoming more widely available, but standard criteria for bioequivalence require only that a single study in healthy volunteers demonstrate that mean pharmacokinetic parameters fall within 80–125% of the mean values for Neoral, the reference formulation of CsA. However, CsA absorption is known to differ between healthy volunteers and transplant patients and between different types of transplant patients, such that standard bioequivalence testing may be inadequate to ensure interchangeability of CsA formulations in all patients. The limited available clinical evidence has shown that stable renal transplant patients receiving Neoral have a significant reduction in mean CsA trough level after transfer to the Cicloral formulation. Mean pharmacokinetic values have been reported as equivalent following transfer to Gengraft in one study, but mean CsA trough fell and mean serum creatinine rose significantly in a separate trial. The only clinical outcomes data available are from a retrospective study of de novo renal transplant patients, which reported a significantly higher incidence of biopsy-proven acute rejection in patents receiving Gengraf versus Neoral (39% versus 25%, $P < 0.05$). Until robust clinical data demonstrate that different formulations of CsA are interchangeable, it is advisable to prescribe CsA by brand, and any transfer to a different CsA formulation should be undertaken with close supervision and only at the direction of the transplant physician.

Keywords Cyclosporine · Bioequivalence · Generic

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Introduction

Cyclosporine A (CsA) represents the cornerstone of immunosuppression for many tens of thousands of transplant recipients worldwide, the vast majority of whom receive the microemulsion formulation Neoral. Recently, new formulations of CsA have been developed by generic manufacturers, some of which are already available commercially in many countries. It is realistic to expect that more generic formulations will be marketed in the foreseeable future.

Use of generic formulations is appropriate and cost-effective for many types of medications and, indeed, is to be encouraged as healthcare budgets face increasing demands. Clinical considerations regarding efficacy and safety, however, must be paramount when evaluating use of a generic product. For drugs such as CsA, which exhibit complex absorption patterns and for which maintaining therapeutic exposure levels is critical to patient well-being and survival, it is incumbent upon health professionals to scrutinize the available pharmacokinetic and clinical data carefully before prescribing new generic formulations.

In 1999, a group of transplant clinicians and pharmacokinetics specialists met to review the evidence available at that time regarding use of generic CsA formulations. The group's conclusions were published as guidance for transplant clinicians and pharmacists [1]. Since that time, additional clinical data has become available that advances our understanding of the potential implications associated with transferring patients between different formulations of CsA. As members of the original group, we have now compiled the following article to assess the most up-to-date evidence concerning the use of generic formulations of CsA in the stable transplant recipient.

Absorption of CsA

CsA is a highly lipophilic molecule that exhibits limited and highly variable absorption [2]. It has been shown that renal transplant recipients with low CsA bioavailability are at higher risk for graft loss [3] and that those who demonstrate marked variability in CsA exposure are more likely to experience chronic rejection [4]. Moreover, because CsA has a narrow therapeutic window, small changes in dose or absorption can result in patients experiencing either rejection, as a result of underimmunosuppression, or CsA-related toxicity, such as renal dysfunction, due to overimmunosuppression. Either of these impacts adversely on the patient's risk of chronic allograft rejection or graft loss [5, 6, 7].

To address these issues, the microemulsion formulation of CsA, Neoral, was developed. Neoral has markedly different absorption characteristics than the original oil-based Sandimmune formulation [8], with significantly higher mean values for drug exposure (AUC_{0-12}), trough concentration and peak concentration [9].

Limitations of bioequivalence criteria

Standard criteria have been defined by several regulatory bodies [10, 11] for generic formulations of all prescription medications, regardless of drug type or therapeutic category. These require that a study be carried out in which healthy young volunteers are given a single dose of the reference formulation and the generic formulation that is being tested. The 90% confidence interval for the mean peak concentration (C_{max}) and the mean drug exposure (AUC) using the generic formulation is within 80–125% of the mean values for the reference brand of the drug (in this case, Neoral) in the single-dose study [10, 11]. The standard bioequivalence criteria do not require the generic formulation to be evaluated in patient populations or in the steady state.

In the solid organ transplant setting, these limitations give cause for concern [12]. CsA absorption differs between healthy volunteers and transplant recipients [13]; indeed, absorption varies in transplant recipients depending on time after transplantation and depending on the type of organ graft [2, 14, 15]. Moreover, patient characteristics such as age [16, 17], ethnicity [18, 19] or co-morbid disease [18, 20, 21] also affect the extent of CsA absorption.

The inability of standard testing to confirm bioequivalence in a transplant population under real-life conditions was demonstrated in the case of the SangCyA formulation of CsA. This formulation was licensed in the USA on the basis of a single study in healthy volunteers. Subsequently, the SangCyA solution was withdrawn after it was found not to be bioequivalent to Neoral oral solution when taken with apple juice [22]. A further example occurred with the introduction of soft gelatin capsules of the Sandimmune formulation. Studies in healthy volunteers and in kidney transplant recipients [23] showed that the oral solution of Sandimmune was bioequivalent to the soft gelatin capsule formulation. However, in a study of 20 maintenance renal transplant recipients known to be poor absorbers of CsA, the oral solution showed 38% higher peak CsA concentration, on average ($P < 0.01$) and 11% greater total exposure than the capsule formulation ($P = 0.09$) [24]. Differences in trough levels were less marked between the two formulations.

Pharmacokinetic comparison of available CsA formulations

Preclinical evidence

There has been very little testing of generic formulations of CsA in animal models. One study, conducted in a rat model [25], compared the bioavailability of the Neoral

formulation and the Eon formulation of CsA at steady state. The Eon formulation has been classified as bioequivalent to the Neoral formulation by the Food and Drug Administration (FDA). The bioavailability of Eon was found to be 15% lower than with Neoral (AUC 27.9 ± 3.69 mg h/l versus 32.1 ± 4.32 mg h/l) using a dose of 10 mg/kg q.d., although this difference was not statistically significant. Interestingly, the pattern of metabolite production differed between the two formulations: plasma levels of the first-pass CsA metabolite AM4 N were higher with Eon than with Neoral while the primary metabolite AM1 was increased in the kidneys of rats receiving Eon. While the clinical significance of these differences in metabolic patterns is not clear, these findings suggest that the carrier agents in the formulation may play some role in CsA pharmacokinetics rather than being purely inert [26]. This leads to the question of whether formulation excipients might interact if patients were allowed to mix different formulations of CsA without an adequate wash-out period, an issue that merits investigation in the clinical setting.

Studies in healthy volunteers

Eon formulation

The cross-over study in healthy volunteers that was undertaken to support approval of the Eon formulation as bioequivalent to Neoral reported that both C_{max} and CsA exposure (AUC) are significantly lower using the Eon formulation than with Neoral if identical doses are used ($P < 0.05$) [27]. Just under a fifth of volunteers (17%) had AUC values less than 80% of that seen when given a dose of Neoral, and 38% had C_{max} less than 80% recorded with Neoral [26].

A comparison of individual pharmacokinetic parameters among 34 patients receiving the Eon and Neoral formulations in a cross-over study [27] has shown that 17.6% of patients were found to be underexposed as measured using AUC, and 38.2% of patients were found to be underexposed as measured using C_{max}, when compared with the 90% confidence intervals for AUC and C_{max} with Neoral [27].

It is relevant to note that when healthy volunteers are administered Neoral at the same time as food, CsA exposure is reduced compared with when taken fasting [28]. In contrast, CsA absorption is 12% higher with the Eon formulation when taken with food than with fasting [29].

Gengraf formulation

Similarly, with the Gengraf formulation of CsA, results in healthy volunteers showed that both C_{max} and AUC values were significantly lower than for Neoral ($P < 0.05$) [29], despite meeting FDA criteria for bioequivalence. As with Eon, when Gengraf is taken with food, CsA exposure increased by 12% compared with when it was taken in the fasting state [30], in contrast to a fall of 18% when the Neoral formulation is taken with food.

Studies in transplant patients

Currently, there is a paucity of data relating to the efficacy and safety of transferring transplant patients from the reference Neoral formulation to a generic formulation or, indeed, from one generic form of CsA to another.

Cicloral (Hexal) formulation

A multicenter study [31] of 41 long-term renal transplant patients has been carried out to assess the effect of switching from the Neoral to the Cicloral formulation. All patients had stable graft function and were more than 1 year post-transplant, receiving dual or triple therapy. A minimum of three CsA trough levels

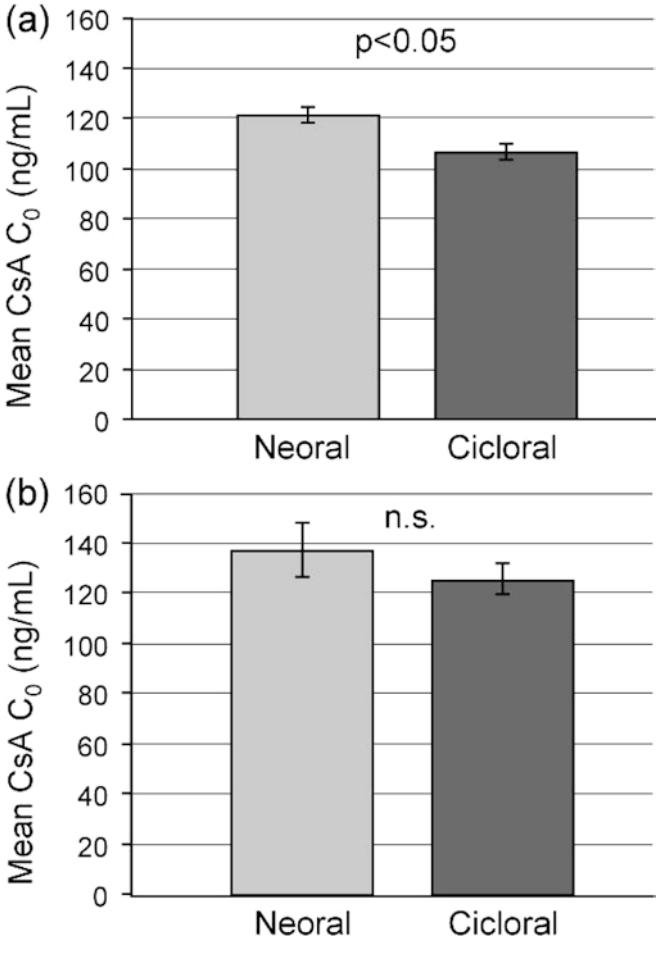

Fig. 1 Cyclosporine (CsA) trough (C_0) level in stable renal transplant patients more than 1 year post-transplant before and after switch from Neoral to the Cicloral formulation of CsA for 18 patients with no dose change (**a**) and 13 patients in whom dose was changed (**b**). Values shown are mean ± SD [31]

were recorded before and after switch to Cicloral. Among 18 patients in whom the dose remained unchanged during and after the switch, 13 showed a fall in CsA trough level and 4 showed a rise. Overall, there was a significant fall of more than 13% in mean CsA trough level (121 ng/ml to 106 ng/ml, $P < 0.05$) (Fig. 1). Data on AUC and CsA peak concentration were not provided.

Gengraf formulation

Two studies have assessed the effect of transferring stable renal transplant patients from the Neoral to the Gengraf formulation of CsA. In the first of these [32], 50 patients were transferred from Neoral to Gengraf for a period of 2 weeks, then were transferred back to Neoral on a 1:1 dose ratio. This trial found no significant difference in the mean pharmacokinetic measurements during the three periods of the study, and the investigators found no need for dose adjustments in any patient. The authors concluded that the pharmacokinetics of Gengraf are equivalent to those of Neoral. However, only mean values of pharmacokinetic parameters were provided [C_{max}, trough blood concentration (C_0), AUC and time to maximum blood concentration (t_{max})], without any individual data or ranges. Thus, it is not possible to determine from this short-term study what proportion of patients was outside the acceptable range of variation from mean Neoral values or individual variation in pharmacokinetic parameters when switched from one formulation to another.

In a second study [33], long-term renal transplant patients were randomized to remain on Neoral ($n = 9$) or switch to Gengraf ($n = 73$) and were followed for 4–8 weeks with serum creatinine measurements taken 1–3 months later. Of 73 patients, 13 (18%) required a dose change after transfer to Gengraf. Mean CsA trough level in all patients converted to Gengraf rose significantly, from 180.5 ± 8.4 ng/ml to 195.0 ± 9.8 ng/ml ($P < 0.05$). At the same time, mean serum creatinine increased significantly ($P < 0.05$), but the extent of the rise may not have been clinically relevant (Fig. 2). Among patients receiving a dose change, there was no significant difference in trough levels or serum creatinine levels 2–4 weeks after the dose modification. No dose changes were required among the patients who remained on Neoral.

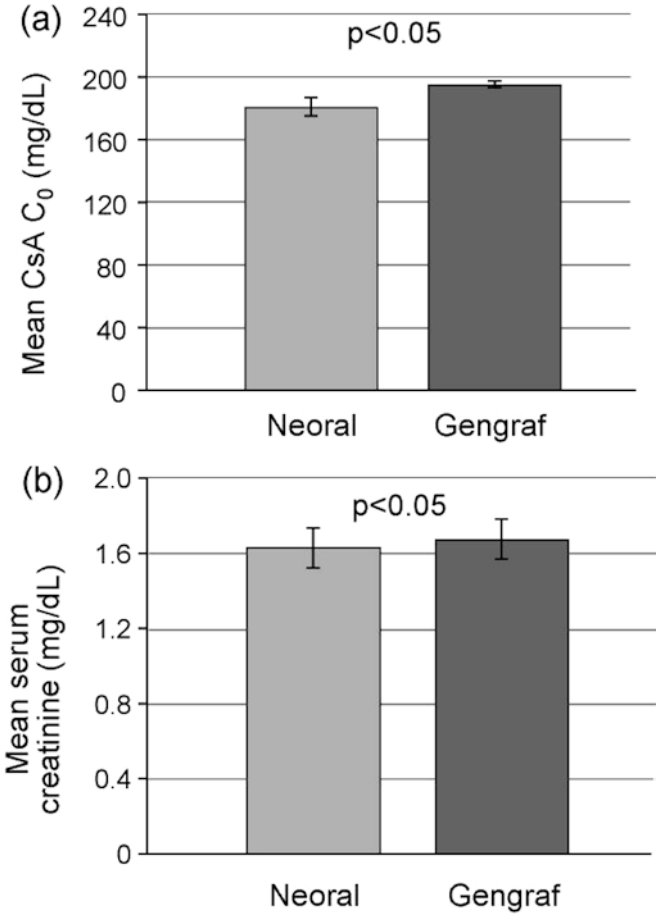

Fig. 2 Cyclosporine trough (C_0) (**a**) and serum creatinine (**b**) among 73 stable renal transplant patients while receiving Neoral and 2–4 weeks after transfer to Gengraf. Values are mean ± SD [33]

Impact of CsA formulation on clinical outcome

Historically, comparisons between Neoral and the original Sandimmune formulation have shown that differences in CsA pharmacokinetics can translate into differences in clinical outcome. A meta-analysis [34] of 930 de novo renal transplant patients demonstrated a significantly lower incidence of acute rejection with Neoral than Sandimmune (35% versus 50%, $P < 0.05$). A large-scale registry analysis has also shown significantly poorer graft survival using the Sandimmune formulation than with Neoral [35].

There is a lack of clinical outcomes data using more recent formulations of CsA. The only reported study is a retrospective analysis of biopsy-proven rejection rates at a single center among 188 de novo renal transplant recipients [36]. Between January 1999 and April 2001, 100 patients received Neoral; from May 2001 onwards, the Gengraf formulation was used ($n = 88$). All patients received mycophenolate mofetil, steroids and induction therapy. The patient groups were well matched in terms of age, race, panel reactive antibody status, human leukocyte antigen mismatch and cold ischemia time, and there were no differences in patient or graft survival at 6 months. However, biopsy-proven rejection rates at 6 months were significantly higher with the Gengraf formulation (39%) than with Neoral (25%, $P < 0.05$) (Fig. 3a). The mean trough concentrations of CsA did not differ significantly between the two formulations, but the authors comment that there appears to be more variability in the Gengraf group during the early post-transplant period (Fig. 3b).

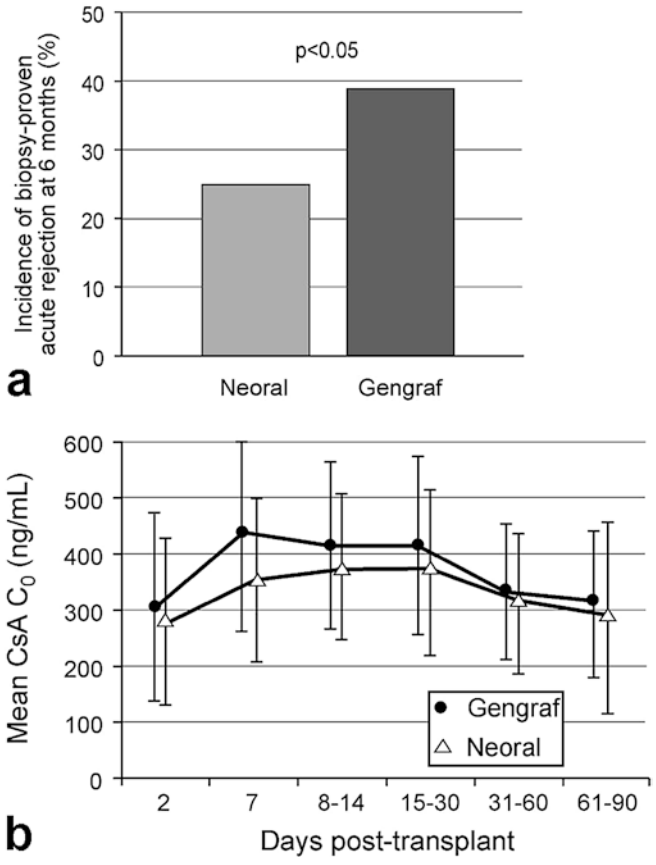

Fig. 3 Incidence of biopsy-proven acute rejection at 6 months (**a**) and cyclosporine trough (C_0) levels to 3 months post-transplant (**b**) among 188 de novo renal transplant recipients receiving Neoral ($n = 100$) or Gengraf ($n = 88$) in a retrospective study [35]

To our knowledge, no clinical studies exist that evaluate the efficacy or safety of transferring long-term transplant recipients from Neoral to another formulation of CsA, or between two generic formulations. Neither has any trial been undertaken in pediatric transplant recipients; however, it would seem prudent to delay evaluation of new formulations in this special group with its particular pharmacokinetic characteristics until data confirming clinical equivalence has been generated in the adult population.

Practical issues relating to CsA formulation

Until robust clinical data demonstrates that different formulations of CsA are interchangeable, it is advisable to prescribe CsA by brand, as is already recommended in some countries [37]. Moreover, any change in formulation should not occur without approval from both the physician and the patient. The importance of this has been highlighted by anecdotal reports of patients receiving Neoral who were inadvertently transferred to the Apotex formulation of CsA, which has a pharmacokinetic profile similar to Sandimmune and could, therefore, be expected to result in significantly different exposure and peak CsA levels [8] and potentially inferior protection against rejection [34].

Where a generic formulation is substituted for Neoral:

a. The switch should only be performed under the supervision of the transplant physician
b. CsA blood levels should be monitored closely during the first weeks after a change of formulation, and dose changed as necessary to maintain consistent absorption
c. The frequency of serum creatinine and blood pressure monitoring should be increased following a change in formulation
d. C_2 monitoring has been evaluated comprehensively for Neoral in adult recipients of solid organ allografts, but only very limited data are available to date on the validity of this approach with generic formulations [38]
e. Different formulations should not be used in the same patient to avoid variation in exposure and also because interactions between excipients have not been studied
f. Particular care should be exercised when considering a switch of CsA formulation in patients with cystic fibrosis, diabetes or cholestasis, since the risk of significant variation in CsA pharmacokinetics using difference formulations appears to be high in these patient types
g. In view of the absence of bioequivalence or clinical data in pediatric transplant recipients, CsA formulations should not be switched in children

Conclusion

CsA is a "critical-dose" drug for which small variations in exposure may have far-reaching clinical consequences for transplant patients. The FDA of the USA prefers the term "narrow therapeutic range drug" and defines these products as "those containing drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation" [11]. CsA is clearly a narrow therapeutic-range drug as defined by the FDA. In its Guidance for Industry on bioequivalence, the FDA recommends "that sponsors consider additional testing and/or controls to ensure the quality of drug products containing narrow therapeutic range drugs. The approach is designed to provide increased assurance of interchangeability for drug products containing specified narrow therapeutic range drugs."

However, the FDA guidance does not elaborate what "additional testing and/or controls" could or should be carried out to assure the interchangeability for drug products. The Expert Advisory Committee on Bioavailability and Bioequivalence of Health Canada [39] takes the view that critical-dose drugs require stringent

bioequivalence requirements and that the bioequivalence "goal-posts" should be narrowed for these drugs. The committee suggested a 90% confidence interval of 90–112% for the percentage ratio test to reference rather than the FDA's [11] and CPMP's [10] much wider limits of 80–125%. This would go some way toward ensuring interchangeability of critical-dose drugs.

It is clear from the data that are beginning to emerge that using the FDA's [11] and CPMP's [10] current bioequivalence limits for standard bioequivalence testing undertaken in healthy volunteers cannot be relied upon to ensure that CsA pharmacokinetics are therapeutically equivalent in individual transplant patients. Currently, there is a lack of comparative data relating to the pharmacokinetics of the reference formulation Neoral and generic formulations in transplant recipients, but the weight of data currently available indicates that generic formulations are not therapeutically equivalent to Neoral in a significant proportion of patients. Robust bioequivalence studies in different types of transplant patients are urgently required if we are to avoid "bodies lying in the streets" [40].

Prospective clinical studies investigating the efficacy and safety of generic formulations in both de novo and long-term transplant patients are also awaited, particularly in light of recent retrospective evidence that rejection rates may be higher using the Gengraf formulation than Neoral in newly-transplanted patients. No outcome data exists concerning the transfer of long-term patients to generic formulations.

Until further evidence is available on the transfer of transplant patients to or between generic formulations of CsA, any transfer to a different CsA formulation should be undertaken with close supervision and only at the direction of the transplant physician.

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