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Improved cyclosporine pharmacokinetics in maintenance renal transplant recipients converted to cyclosporine for microemulsion

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Abstract *Background:* Variability in cyclosporine drug exposure of $\geq 20\%$ has been shown to be a risk factor for the development of chronic renal allograft rejection. We tested the hypothesis that a cyclosporine microemulsion (CsA-ME) would result in reduced variability in stable maintenance renal transplant patients when compared with the original formulation of cyclosporine (CsA).
Methods: The 31 maintenance renal transplant recipients were part of a multicenter, randomized, double-blind, prospective study comparing the CsA formulation with the CsA-ME formulation. Pharmacokinetics analyses were performed at two centers 1, 4, 12, and 52 weeks after patients were randomized to continue receiving CsA or to convert to CsA-ME.
Results: The means of the week 1-, 4-, and 12-week areas under the concentration-time curves (AUC), and Cmax were significantly higher and the Tmax was significantly shorter in those patients converted to CsA-ME than in those remaining on CsA. There was no correlation between change in AUC after conversion and change in serum creatinine. The coefficient of variation values for dose-adjusted AUC, expressed as a percentage ($\%CV_{AUC}$), were lower in CsA-ME patients than CsA patients after both 12 and 52 weeks. Over the initial 12 weeks, $\%CV_{AUC}$ values of $\leq 20\%$ were seen in a significantly greater proportion of CsA-ME patients than CsA patients.
Conclusions. Conversion of maintenance renal transplant recipients from CsA to CsA-ME resulted in improved absorption of cyclosporine. The CsA-ME formulation resulted in long-term reduction in the variability of cyclosporine exposure and more consistent pharmacokinetics.

Key words Cyclosporine microemulsion · Kidney transplant · Pharmacokinetics

Introduction

Variations in cyclosporine pharmacokinetics, particularly absorption, affect clinical management strategies for renal transplant recipients [1]. The absorption and bioavailability of cyclosporine from the traditional formulation (CsA) is inconsistent. Cyclosporine exposure as assessed by area under the concentration-time curve (AUC) is more variable in patients receiving CsA compared with those receiving the cyclosporine from a microemulsion formulation (CsA-ME) [1–4]. In a 12-month prospective randomized study, Wahlberg et al. [2] determined that the intraindividual coefficients of

Abbreviations *CsA* original formulation of cyclosporine (Sandimmune Soft Gelatin Capsules, cyclosporine capsules, USP). *CsA-ME* new formulation of cyclosporine for microemulsion (Neoral Soft Gelatin Capsules, cyclosporine capsules for microemulsion)

variation for AUC, expressed as a percentage (%CV_{AUC}), were significantly higher in 12 maintenance renal allograft recipients maintained on CsA than in 45 patients converted to CsA-ME (23.3% versus 16.7%, $P < 0.001$). The mean time posttransplantation for these patients was not reported. This result is consistent with the findings of previous crossover study with 2-week treatment periods in which intraindividual %CV_{AUC} values of 18% and 10% were reported for CsA-treated and CsA-ME-treated patients, respectively ($P = 0.015$) [3]. At study entry, the time posttransplantation for the 55 patients was between 7 months and 8.8 years. In both of these studies, the %CV was calculated from the mean squared error from ANOVA on the replicate pharmacokinetic values.

Variability in cyclosporine exposure is an important factor to consider for long-term renal graft outcome since it has been demonstrated that > 20% variability in dose-adjusted AUC is a risk factor that contributes 27% to the overall risk for chronic rejection [5]. This effect is equivalent to the contribution of a previous acute rejection episode and greater than that of African-American race, acute tubular necrosis at the time of transplant, or diastolic hypertension [5]. Further data analysis in that study showed that patients who experience a > 25% variation in dose-adjusted AUC are at increased risk of chronic graft rejection [6]. Estimates of the proportion of renal transplant recipients receiving CsA who demonstrate substantial variation in dose-adjusted AUC vary from more than one-third (experiencing > 30% CV) to 70% (experiencing > 20% CV) [6]. Consequently, such variability in cyclosporine exposure may represent a risk factor for chronic rejection for a significant number of CsA-treated patients.

Materials and methods

The study was approved by the institutional review boards at each participating center. The patient demographics and design of this multicenter, randomized, double-blind, prospective, parallel-group trial have been previously reported [7]. Briefly, 300 patients were enrolled at 19 centers in the United States. All patients had stable renal function (established by a stable serum creatinine level of ≤ 2.5 mg/dl) and had not experienced a rejection episode during the 6 months prior to randomization. A 1-month screening period was used to confirm stable renal function; during this period, a change in the serum creatinine value of ≥ 20% was an exclusion criterion for the study. All patients continued to receive CsA during the screening period (at doses of 2 to 10 mg/kg per day). Measurements of whole-blood cyclosporine levels were used to establish baseline target trough levels (C_{min}) for each individual participating in the study. Cyclosporine doses were adjusted during the blinded treatment phase to maintain individual blood levels within these baseline target ranges.

Patients were randomized at a 1 : 1 ratio to receive either CsA or CsA-ME (dispensed as identical-looking soft gelatin capsules) starting on day 0 of the treatment phase. Pharmacokinetic parameters were evaluated in a subset of these patients ($n = 31$) from two centers on weeks 1, 4, and 12 after randomization, and a final evaluation was performed on week 52 at one center ($n = 13$). At the time of the pharmacokinetic testing, the patients were admitted to the research hospital. After an overnight fast, the dose of cyclosporine was given at 7 a.m. Blood specimens were obtained just before and at 0.33, 0.66, 1, 1.5, 2, 2.5, 3, 4, 6, 9, and 12 h after the dose of cyclosporine. A standardized breakfast, lunch, and snack was given starting 2 h after the morning dose of medication. Cyclosporine blood levels were determined using a parent compound-specific fluorescence polarization immunoassay.

AUC values were calculated using the linear trapezoidal rule; values for peak concentration (C_{max}), time to reach peak concentration (T_{max}), and C_{min} were also determined. All pharmacokinetic parameters (except T_{max}) were dose-adjusted. The intraindividual variability of AUC was determined by calculating %CV values. Comparisons between the two cyclosporine formulations were based on Wilcoxon's rank-sum test. Fisher's exact test was used to compare the frequency of the occurrence of %CV values that were either ≤ 20% in the two cyclosporine treatment groups.

Results

For the subgroup of patients in this pharmacokinetic analysis, the mean age was 38.3 ± 12.2 years in the CsA group ($n = 15$) and 42.3 ± 9.4 years in the CsA-ME group ($n = 16$). Patients in both groups were predominantly Caucasian, with comparable weight and gender distribution. The mean time posttransplantation was 56.2 ± 33.7 months in the CsA group and 67.7 ± 30.9 months in the CsA-ME group.

The %CV of dose-adjusted AUC was reduced in CsA-ME-treated patients compared with CsA-treated patients during the evaluation period up to and including week 12 (Fig. 1 A), and up to and including week 52 (Fig. 1 B). These differences were statistically significant through the 12-week evaluation period ($P = 0.019$). Because of the small sample size at 52 weeks, the difference was not statistically significant ($P = 0.1$).

Further analysis showed that during the first 12 weeks, a significantly greater proportion of patients treated with CsA-ME (87%) compared with those treated with CsA (47%) had a %CV_{AUC} value that was ≤ 20% ($P = 0.023$); (Fig. 2). Thus, 53% of the patients who remained on CsA had a %CV_{AUC} value that was > 20%, vs 13% in the CsA-MEgroup. The reduced variability of cyclosporine exposure in patients converted to CsA-ME was maintained in the subset of patients analyzed at 52 weeks: 83% of CsA-ME-treated and 43% of CsA-treated patients had %CV_{AUC} values that were ≤ 20%. Therefore, %CV_{AUC} values were > 20% in 57% of CsA-treated and 17% of CsA-ME-treated patients, respectively. Because of the small sample size ($n = 6$ for CsA-ME and $n = 7$ for CsA) at 52 weeks, this was not statistically significant.

Conversion from CsA to CsA-ME resulted in improved absorption of cyclosporine shown by the mean pharmacokinetic values obtained at weeks 1, 4, and 12

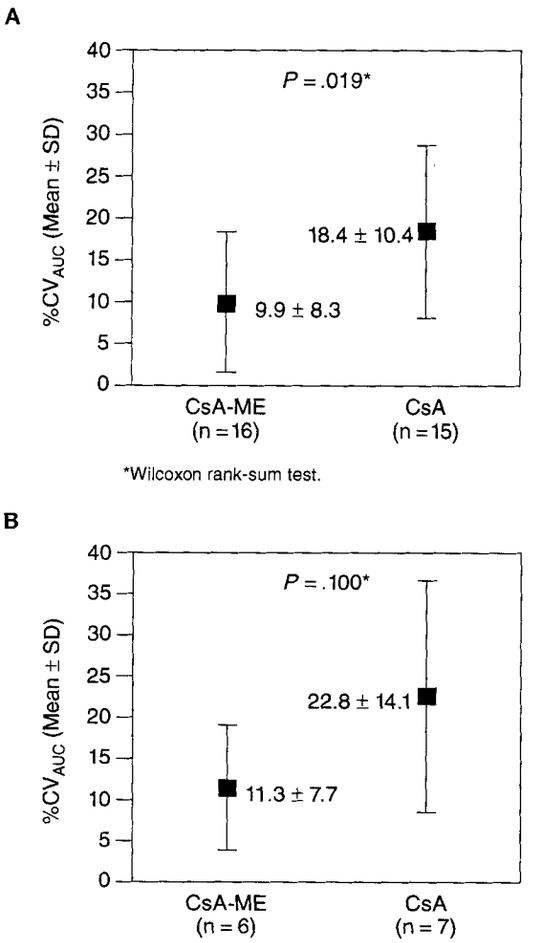

Fig. 1 A, B Intrasubject variability of dose-adjusted AUC in maintenance renal transplant recipients: CsA-ME vs CsA at (**A**) 1, 4, and 12 weeks and (**B**) 1, 4, 12, and 52 weeks

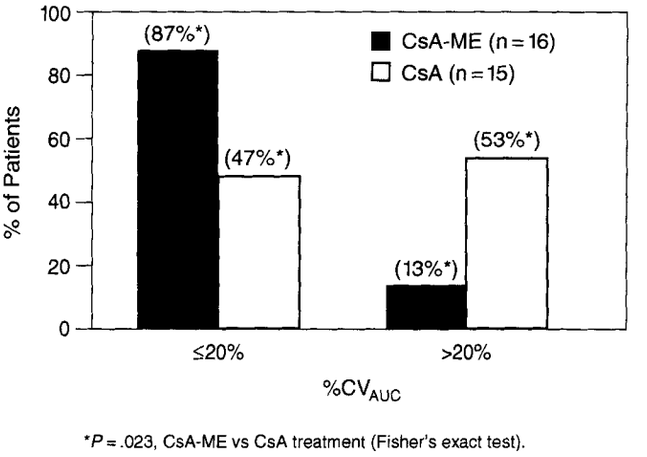

Fig. 2 Comparison of intrasubject variability of the dose-adjusted AUC ($\%CV_{AUC}$) based on pharmacokinetic data obtained on weeks 1, 4, and 12

Table 1 Dose-adjusted pharmacokinetic parameters. Values are the means (weeks 1, 4, and 12) ± SD

Parameter	CsA-ME ($n = 16$)	CsA ($n = 15$)	P-value[a]
AUC (ng · h/ml · mg)	40.6 ± 10.6	29.1 ± 8.2	0.002
C_{max} (ng/ml · mg)	10.5 ± 3.3	6.3 ± 2.0	0.0003
C_{min} (ng/ml · mg)	1.28 ± 0.4	1.0 ± 0.4	0.06
T_{max} (h)	1.65 ± 0.4	2.2 ± 0.6	0.004

[a] Based on Wilcoxon's rank-sum test

for AUC, C_{max}, C_{min}, and T_{max} (Table 1). With the exception of C_{min}, which was not an independent variable as it was set by study, all pharmacokinetic differences between formulations were statistically significant. Changes in the pharmacokinetic parameters were present by 1 week after conversion (data not shown).

Assessment of safety parameters at 1 year indicated that the two formulations were comparable in safety and tolerability. Mean changes from baseline in serum creatinine values and blood pressure readings were similar in both treatment groups. Furthermore, within those patients converted to CsA-ME, there was no correlation between the degree of change in AUC and serum creatinine, when comparing those values obtained at baseline (on CsA) and week if (on CsA-ME; Fig. 3). There was one biopsy-proven acute rejection. This occurred in a patient receiving the CsA formulation who had a $\%CV_{AUC}$ value of > 20 %. The incidence of newly occurring or worsening adverse events was also comparable in the two treatment groups.

Discussion

These results clearly confirm that in renal transplant recipients, cyclosporine exposure after administration of CsA is inconsistent even as long as 4.5 years after transplant. Conversion of CsA-ME maintenance therapy significantly reduced this variation in AUC compared with patients who continued to receive CsA. This improvement persisted over a period of at least 12 months. This may have important clinical ramifications, since it has been demonstrated that variability in cyclosporine exposure is a risk factor for chronic rejection. The reduction in the intraindividual %CV value for dose-adjusted AUC to < 20 % that occurred in the majority of patients converted to CsA-ME might result in a reduced incidence of chronic graft rejection [5]. A significant higher proportion of CsA-ME-treated patients in the present study fell into this category (87 %) compared with those receiving CsA (47 %), and these patients may therefore

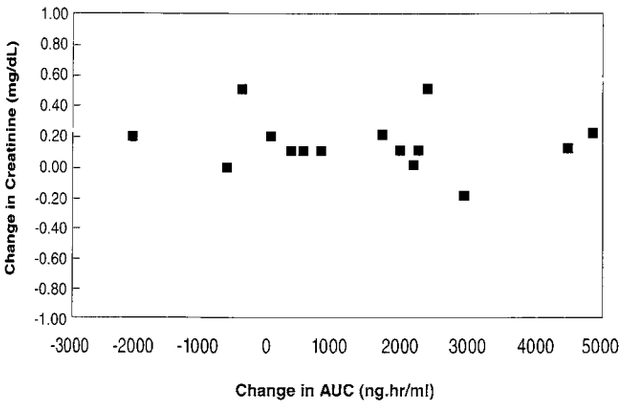

Fig. 3 Correlation between change in AUC and change in serum creatinine from baseline to week 4 in those patients converted to CsA-ME

receive additional benefit from the more consistent exposure to cyclosporine from the CsA-ME formulation.

In summary, the CsA-ME formulation reduced the intrapatient variability of cyclosporine exposure compared with the CsA formulation, with a comparable safety profile. By reducing this important risk factor, CsA-ME has the potential to minimize the risk of chronic rejection.

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