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Ferda M. Şenel
Sedat Yildirim
Hamdi Karakayali
Gökhan Moray
Mehmet Haberal

Comparison of Neoral and Sandimmun for induction and maintenance immunosuppression after kidney transplantation

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F. M. Şenel · S. Yildirim · H. Karakayali
G. Moray · M. Haberal (✉)
Baskent University,
Department of Surgery,
Fevzi Cakmak Caddesi, 10. Sokak No:45,
TR- 06490 Bahcelievler, Ankara, Turkey,
Fax: + 90 312 223 7333

Abstract We compared the mean trough level/dose (L/D) ratio, mean coefficient of variation (CV) of individual patients, and graft, patient, and rejection-free survival rates of 40 renal transplant recipients receiving Neoral (CyE) with 103 consecutive renal transplant recipients receiving Sandimmun (CyA). The mean L/D ratio on the 3rd post-transplant day (16.2 vs 11.8, $P < 0.04$), in the 1st week (24.6 vs 16.1; $P < 0.03$), and 1st month (39.1 vs 28.7; $P < 0.05$) were higher in the CyE group. In both groups the L/D ratio improved in proportion to the duration of time post-transplant and reached a maximum in the 3rd post-transplant month. In the early post-transplant period in particular, the number of patients achieving target levels was significantly higher, and the mean dose needed to achieve target levels lower, in the CyE group. The variation in trough levels, demonstrated by the CV, was lower in the CyE group (0.41 ± 0.14) than in the CyA group (0.62 ± 0.21; $P < 0.005$). Actuarial 1-year patient and graft survival rates in the CyE group were 100 % and 96 %, respectively; these were similar to the 100 % and 95 % in the CyA group. The 1-year rejection-free survival rate in the CyE group was 61 % compared to 43 % in the CyA group ($P < 0.02$). We conclude that it is possible to obtain higher blood trough levels at lower doses by administering CyE, particularly in the early post-transplant period. The lower variability of trough levels and the higher L/D ratio in the CyE group, which are related to improved bioavailability of CyE, may explain the lower rejection rate among these patients. In this study, the microemulsion formulation of cyclosporin (CyE) was found to be more beneficial and cost-effective as induction and maintenance immunosuppression than the conventional formulation (CyA).

Key words Immunosuppression, kidney transplantation, Neoral · Neoral, kidney tranplantation, immunosuppression

Introduction

Cyclosporin (CyA) was extracted from Tolypocladium inflatum Gams, which was obtained from soil samples in Norway in 1969. The discovery of the immunological activity of the compound by Borel et al. [2] led to trials in clinical renal transplantation [4]. Since its approval for clinical use, CyA has become the central component of most immunosuppressive regimens and has improved the survival of all types of allografts. There is considerable interindividual variation in the bioavailability of CyA, i.e., 1 %–67 % with an average of 30 % [5]; in drug clearance rates, it varies from 2 to 32 ml/min per kg [6, 7]; and in average time to peak blood concentration after oral administration from 1 to 8 h with a mean of 3.8 h [5]. The drug has a half-life that varies from 4.2

to 34.6 h [10, 16]. A pharmacokinetic study of oral CyA administration documented a 38 % coefficient of variation (CV) in dose-adjusted AUC, with an absolute intraindividual difference in daytime AUC (0–12 h) from 2 % to 54 % (mean 30 %) and night-time AUC(0–12 h) from 5 % to 80 % (mean 34 %) [17]. The pharmacokinetic parameters $t_{1/2}$, T_{max}, and C_{max} were more variable than the AUC during both the day and night.

A microemulsion formulation of CyA (CyE, Neoral; Sandoz, Basel, Switzerland) displays improved bioavailability, particularly in the immediate postoperative period. Unlike the olive oil-based liquid and corn oil-based gel caps that must be digested by pancreatic enzymes and emulsified by bile into hydrophilic particles [14], its ready dissolution upon contact with aqueous fluids without requisite actions of bile, enzymes, or small intestinal secretions produces an increased oral bioavailability [15] and a reduced intra-, and possibly inter-, individual variation in pharmacokinetic parameters. The time to achieve target concentrations (T_{max}) is also significantly lower with CyE.

In the current study, we compared renal transplant recipients receiving CyE with patients receiving CyA as induction and maintenance immunosuppression in addition to azathioprine (AZA) and prednisolone (pred).

Materials and methods

Patients

A total of 143 patients receiving a renal allograft between January 1993 and April 1996 were included in the study. The mean trough level (ng/ml) to dose (mg/kg) ratio (L/D ratio), CV, and patient, graft, and rejection-free survival rates of 40 patients transplanted between January 1995 and April 1996 who were receiving the microemulsion formulation (CyE) were compared with those of 103 patients transplanted between January 1994 and December 1994 who were receiving the conventional cyclosporin formulation (CyA). The mean follow-up periods of patients in the CyA and CyE groups were 29.7 ± 5.1 and 12.7 ± 4.6 months, respectively. Patient demographics, such as age, gender, HLA match, donor source, and mean cold ischemic time were similar. The mean age in the CyA group was 33.6 ± 8.2 (range 8–62) years and in the CyE group 35.2 ± 7.9 (range 11–54) years. In the CyA group, 31/103 (30 %) received cadaver kidneys, as did 13/40 (33 %) in the CyE group. The mean cold ischemic time of the cadaver kidneys in the CyA group (13.2 ± 8.4 h) was similar to that in the CyE group (15.7 ± 7.9 h). Two patients in the CyA group and one patient in the CyE group received a second graft. The mean HLA match was 2.8 in the CyA group and 3 in the CyE group.

Immunosuppression

In addition to CyA or CyE, 5 mg/kg, given in two divided doses (q 12 h), all patients received AZA, 2 mg/kg, and pred, 1 mg/kg, which was tapered to 20 mg/day on postoperative day 10, and to 10 mg/day by the 4th postoperative month. Blood trough levels of CyA and CyE were monitored using the monoclonal TDX technique. Dose adjustments of CyA and CyE were made according to blood trough levels (C_{min}). The target C_{min} value for the 1st post-transplant month was between 200 and 250 ng/ml, and between 150 and 200 ng/ml after this period. For both CyA and CyE groups, C_{min} levels were measured every day before the morning dose during the 1st post-transplant week, three times per week during the 2nd week, and then twice weekly until the end of the 1st month. Up until the 3rd post-transplant month, C_{min} levels were measured twice per month, and once per month afterwards. There was not any discontinuation or conversion of CyA or CyE to other immunosuppressive agents such as FK 506 or sirolimus.

Acute rejection

A total of 72 patients experienced 82 acute rejection episodes, 52 biopsy-proven and 30 presumptive. Biopsies were performed with an 18-gauge biopsy needle under ultrasound guidance. Histopathological diagnosis of rejection was based on the Banff classification. All acute rejection episodes were treated with methylprednisolone, 500 mg/day for 3 days, and OKT3 or ATG for steroid-resistant acute rejections.

Statistical analysis

The L/D ratio, CV (standard deviation/mean) of individual patients, and graft, patient, and rejection-free survival rates of 52 patients receiving CyA were compared with those of 40 renal transplant recipients receiving CyE using Pearson's correlation, Student's *t*-test, the Kaplan-Meier survival curve, and the log-rank test. The chi-square and Student's *t*-tests were used to compare patient demographics. "Excel 5.0" and "SPSS for Windows" programs were used for the statistical analysis.

Results

Level/dose (L/D) ratio

The mean L/D ratio of the patients in the CyA and CyE groups were compared on the 3rd post-transplant day, in the 1st week, during the 1st, 3rd, and 6th months, and at 1 year. The mean L/D ratio on the 3rd post-transplant day in the CyE group was higher than in the CyA group (16.2 vs 11.8, $P < 0.04$). In the CyA group, only 38/103 (37 %) patients maintained target trough levels (between 200 ng/ml and 250 ng/ml) on the 3rd post-transplant day, while in the CyE group 22/40 (55 %) patients had levels equal to or above target trough levels ($P < 0.05$). The mean CyA dose needed in order to achieve the target level on the 3rd post-transplant day was 10.2 mg/kg in the CyE group and 14.8 mg/kg in the CyA group ($P < 0.03$). The mean L/D ratio in the 1st week (24.6 vs 16.1; $P < 0.03$) and 1st month (39.1 vs 28.7; $P < 0.05$) were also significantly higher in the CyE group, which showed that at the same dose as CyA, CyE led to higher C_{min} values. In the 1st post-transplant week, 34/40 (85 %) patients in the CyE group and 70/103 (68 %) patients in the CyA group achieved target trough levels

($P = 0.04$). The dose needed to achieve the target level was 7.2 ng/ml in the CyE group and 11.4 ng/ml in the CyA group ($P < 0.05$). After the 1st post-transplant month, although the mean L/D ratio was higher in the CyE group, these differences were not statistically significant. At 1 month post-transplant, 95 % of the patients in the CyE group and 90 % in the CyA group had C_{min} values equal to or above the target trough level (P = NS). In both groups the L/D ratio improved in proportion to the duration of time post-transplant and reached a maximum during the 3rd post-transplant month, namely, 42.7 for the CyE group and 37.1 for the CyA group (Fig. 1). During the first 3 post-transplant days, there was a weak correlation between C_{min} values and doses (mg/kg) of CyE ($r^2 = 0.32$) and CyA ($r^2 = 0.22$), which improved after the 1st post-transplant week (CyE $r^2 = 0.41$; CyA $r^2 = 0.36$; P = NS). Although the correlation coefficient was not high, CyE had a better L/D correlation than CyA during the entire study period. The correlation coefficients apparently improved on the Neoral formulation, though the difference was not statistically significant.

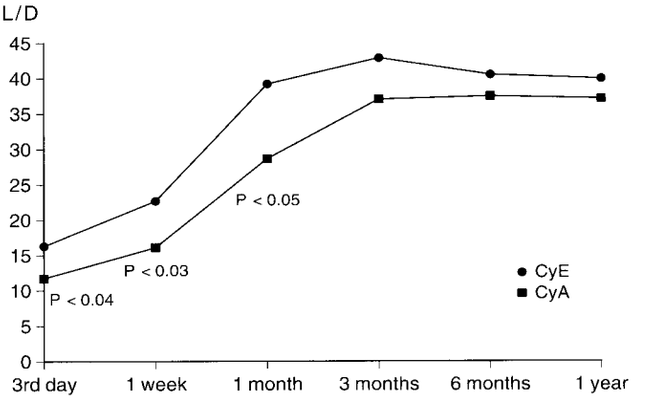

Fig. 1 Level-dose (L/D) ratio of the patients receiving CyA and CyE. Higher blood levels were obtained with lower CyE doses, particularly in the early post-transplant period

Comparison of coefficient of variation (CV) among patients receiving CyA and CyE

The variability of C_{min} values was examined by calculating the CV of individual patients in each group. The mean CV of C_{min} values of patients was lower in the CyE group (0.41 ± 0.14) than in the CyA group (0.62 ± 0.21; $P < 0.005$; Fig. 2). This means that there was less fluctuation of C_{min} values among patients treated with CyE than among those in the CyA group during the whole follow-up period which, in turn, may indicate a lower intraindividual variation in blood CyA levels in the CyE group.

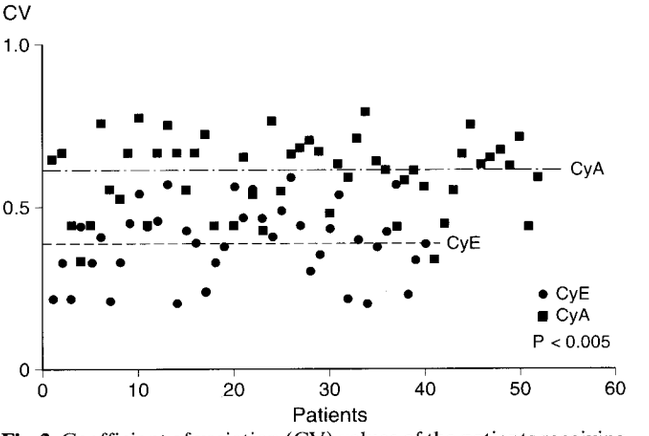

Fig. 2 Coefficient of variation (CV) values of the patients receiving CyA and CyE. *Broken lines* indicate the mean CV of each group (0.6 vs 0.4; $P < 0.005$)

One-year patient, graft, and rejection-free survival rates

Actuarial 1-year patient and graft survival rates in the CyE group were 100 % and 95 %, respectively, which were similar to the 100 % and 94 % in the CyA group. The 1-year rejection-free survival rate in the CyE group was 61 % compared to 43 % in the CyA group ($P < 0.02$; Fig. 3). There was a total of 82 rejection episodes, 18 in the CyE group and 66 in the CyA group. Diagnoses of 52/82 (63.4 %) rejection episodes were made by allograft biopsy; the others were based on clinical criteria (presumptive rejection), i.e., a rise in blood creatinine to more than 30 % over the maximum value in the absence of other reasons, such as sepsis or dehydration. Most of the diagnoses of acute rejection episodes in the CyE group were biopsy-proven (16/18, 88.8 %), while this was only 54.5 % in the CyA group.

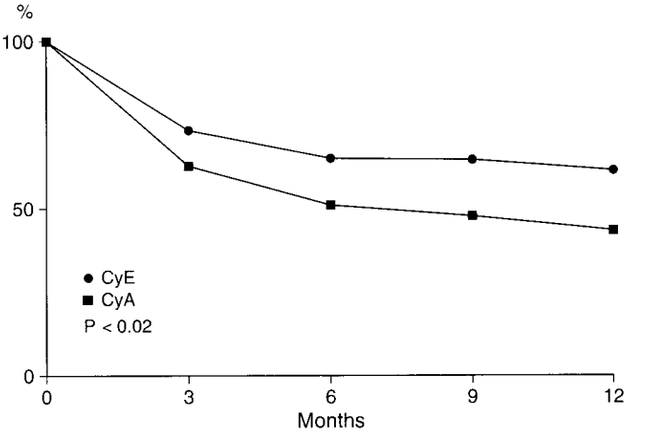

Fig. 3 One-year rejection-free survival rates of patients receiving CyA and CyE

Discussion

CyA has low bioavailability, which is associated with an increased risk of allograft rejection [13]. The high inter- and intraindividual variability of CyA may be related to variable absorption patterns among different individuals. The new oral formulation Neoral (CyE) was developed to improve the absorption of CyA by incorporating the drug in a microemulsion preconcentrate. Following oral administration, CyE forms a microemulsion that can be readily absorbed.

In the present study, we examined the Level/dose relation among patients receiving CyA and CyE. In both groups the Level/dose ratio improved significantly after the 1st post-transplant week and doubled by the end of the 1st post-transplant month. Although the correlation between C_{min} values and administered dose was not strong, higher C_{min} values were obtained in the CyE group with the same dose as that administered in the CyA group during the entire study. Thus, lower CyE doses were required to achieve the same target trough concentration obtained with CyA. A previous study showed a reduced requirement for the microemulsion formulation than for the gel cap CyA formulation to achieve target concentrations during the 1st month (11.99 vs 15.66 mg/kg, $P < 0.05$) [9]. In our study, the mean cyclosporin dose needed to achieve target levels was also significantly lower in the CyE group (10.2 mg/kg) than in the CyA group (14.8 mg/kg). Our results were also significant within the 1st post-transplant month, and this may be related to the improved absorption pattern of CyE, particularly during the immediate post-transplant period, when CyA has low bioavailability. These results show that it may be possible to use lower cyclosporin doses to achieve therapeutic levels which, in turn, would reduce the overall cost of the immunosuppression.

The variability of C_{min} values, calculated as the CV, was high in both groups, but the CV in the CyA group (62 %) was significantly greater than in the CyE group (41 %). The CV value of CyA in the present study was greater than the 38 % CV reported previously by Ohlman et al. [17]. In a previous study by Kovarik et al. [11], it was shown that variability of C_{min} values from the CyE was significantly less, ranging from 10 % to 22 %. The higher variation in C_{min} values in our study may, in part, be due to the weak correlation of C_{min} with the administered dose (CyE $r^2 = 0.41$; CyA $r^2 = 0.36$) and in part to the high intraindividual variation of CyA pharmacokinetics. Although there is considerable interindividual variation in the bioavailability, drug clearance rates, and C_{max} values [5–7] of CyA, CyE displays less variation in these pharmacokinetic parameters [1, 12]. The lower inter- and intraindividual variation in pharmacokinetic parameters of CyE [8, 11] may also explain the lower CV values in this group.

One-year graft and patient survival rates were similar in both groups, which is consistent with recent studies in which CyE was given for up to 24 months [1, 3]. In our study, 12-month rejection-free survival was significantly high in the CyE group (61 %) compared to the CyA group (41 %; $P > 0.02$). The incidence of rejection episodes was found to be similar in patients receiving CyA and CyE in a 12-week multicenter study that included 101 primary renal allograft recipients [1]. The UK Neoral Renal Study Group recently reported a 12-month rejection rate of 41.4 % among 191 patients receiving CyE compared to 54.6 % ($P < 0.03$) in 97 CyA patients [18]. In our study, the lower acute rejection rate among CyE patients may be explained by the improved bioavailability of CyE, particularly in the early post-transplant period, which is shown by higher C_{min} levels obtained with CyE. The lower variability of C_{min} values, also demonstrated in the present study, may be another factor responsible for the low rejection rate in the CyE group. The higher incidence of acute rejection episodes in the CyA group may also be related in part to the lower number of allograft biopsies in this group compared to patients in the CyE group, which could lead to an overestimation of the diagnosis of acute rejection episodes.

To summarize our results, better C_{min} levels were obtained with CyE when used at the same dose as CyA. This may enable us to use at least 5 % less CyE, a very important factor in developing countries such as Turkey, where the cost of treatment is one of the major determining factors in the long-term compliance of transplant recipients. In the present study, CyE was found to be effective in reducing the rate of acute rejection episodes. The lower rejection rate after CyE may also help reduce overall costs by decreasing the length of the hospital stay and of the antirejection treatment. The improved bioavailability of CyE, combined with less fluctuation in C_{min} values during the overall follow-up period, may be the reasons for the high efficacy of the drug. Although a beneficial impact of CyE on graft survival has not yet been demonstrated, the lower acute rejection rate obtained with it may lead to a reduction in chronic rejection and cause improved graft survival in long-term follow-up.

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