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A randomized pilot study of cyclosporin G in renal transplantation

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Abstract. Animal studies have suggested that the analogue cyclosporin G (CyG) may be less nephrotoxic than cyclosporin A (CyA). A pilot study was therefore performed in 10 primary cadaveric renal allograft recipients who were randomized to receive posttransplant immunosuppression with either CyA or CyG. The follow-up time was a minimum of 1 year. One graft was lost in each group. All patients in both groups experienced at least one acute rejection episode. Episodes of acute nephrotoxicity were observed in both groups. Renal function, as assessed by determinations of the serum creatinine level and chromium-ethylene diamine tetra-acetic acid (Cr-EDTA) clearance, did not differ between the two groups. Renal allograft biopsies showed a significantly higher degree of fibrosis in the CyG group than in the CyA group. All CyG-treated patients evidenced laboratory signs of acute liver toxicity, which was dose-dependent and reversible. Today, all CyG-treated patients have been switched to CyA. This study shows that immunosuppression after renal transplantation in man is possible with CyG; however, it does not seem to have any advantages over CyA.

Key words: Immunosuppression – Cyclosporin A – Cyclosporin G – Renal transplantation

Cyclosporin A (CyA) is presently the mainstay immunosuppressive agent [2–4, 6, 11, 21, 22, 31]. However, its nephrotoxic effect is a major concern [25, 27], and efforts have therefore been made to find a less nephrotoxic analogue. In 1982 Traber et al. [35] reported the discovery of Nva^2-cyclosporine, also known as cyclosporin G (CyG). CyG differs from CyA only in being methylated on the second amino acid of the molecule, thereby changing α-aminobutyric acid to L-norvaline [34]. CyG has been shown to possess immunosuppressive and pharmacodynamic properties similar to those of CyA in vitro as well as in animal models [18, 19]. Furthermore, some animal studies have suggested that CyG may be less nephrotoxic than CyA [5, 8, 12, 16, 19]. In view of these encouraging results, a small number of kidney transplant patients have received CyG for short periods [1, 20]. In this paper we report the results of a randomized pilot study comparing CyG with CyA as an immunosuppressant in renal transplant recipients.

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Materials and methods

Patients. Ten patients receiving a cadaveric renal allograft were included in the study. Five patients were randomized to CyG and 5 to CyA. The exclusion criteria were insulin-dependent diabetes mellitus, retransplantation, T-cell panel reactive antibodies in current serum results, and a history of clinical liver disease or pathological liver values during the preceding 12 months. All patients aged 18–65 years who underwent transplantation between October 1989 and March 1990 and who met the criteria were asked whether they wished to participate in the study, and their informed consent was obtained. Only one patient refused to participate. The patient characteristics are summarized in Table 1. The follow-up time was 12–17 months. The study was approved by the local ethics committee and the Swedish Medical Board.

Immunosuppression. All patients received triple-drug immunosuppression with either CyG or CyA, azathioprine, and prednisolone. The standard oral solution of CyA (Sandimmun mixture, 100 mg/ml, Sandoz, Basel) or the standard intravenous preparation of CyA (Sandimmun in Cremophor EL) was used. CyG was supplied in identical vehicles. CyG and CyA were given orally twice daily from the day of transplantation in an initial dose of 10 mg/kg bw per day. The dose was then adjusted according to determinations of the 12-h cyclosporine trough concentrations. The recommended levels of CyA or CyG were 160–240 ng/ml during the 1st month after transplantation, 100–160 ng/ml during the 2nd and 3rd months, and 60–120 ng/ml thereafter. Azathioprine was given in a dose of 2 mg/kg bw per day during the 1st month and 1mg/kg bw per day thereafter. Prednisolone was given in an initial dose of 100 mg/day and then reduced by 10 mg/day until day 9, when a dose of 20 mg/day was reached. The dose was then further reduced until a maintenance dose of 10 mg/day was reached at 3 months. During transplantation a single dose of 500 mg methylprednisolone was given intravenously (i.v.).

Table 1. Patient characteristics

Treatment group	CyG	CyA
No. of patients	5	5
Mean age ± SD (years)	43 ± 5	52 ± 13
Sex M:F	3:2	3:2
End-stage renal disease		
Chronic glomerulonephritis	1	1
Pyelonephritis	2	2
Polycystic kidney disease	1	1
Reflux nephropathy	0	1
Nephrocalcinosis	1	0
Pretransplant blood transfusion		
0	3	3
≥ 1	2	2
Cold ischemia time (h)	13.4 ± 4.6	9.9 ± 8.1
Donor age ± SD (years)	60 ± 4	43 ± 17
Mismatches in HLA-A/B		
0	0	0
1	2	1
2	1	2
3	2	1
4	0	1
Mismatches in HLA-DR		
0	2	0
1	0	3
2	3	2

Cy, cyclosporine

Diagnosis of acute rejection and nephrotoxicity. Acute rejection episodes were diagnosed by clinical criteria in combination with positive findings from fine needle aspiration biopsies (FNAB) and/or core needle biopsies. Acute rejections were treated with i. v. pulses of methylprednisolone for 4 consecutive days (total dose 1.25 g). If this treatment was insufficient, antithymocyte globulin (ATG, Fresenius, FRG) was given i. v. for 7 days in a dose of 3 mg/kg bw.

Acute cyclosporine nephrotoxicity was assumed to exist if there was an increase in serum creatinine that had no other cause and the biopsy showed isometric vacuolization of the tubular epithelium.

Analyses. Whole blood sampling for analyses of the CyA and CyG levels was performed 10–12 h after dosing. Sampling was performed 3–5 times weekly until discharge, then twice weekly during the first 3 months and thereafter at each outpatient visit (once to twice monthly). The CyA was analyzed by specific monoclonal radioimmunoassay (RIA; Incstar Cyclotrac-SP). The intra- and interassay coefficients of variation for this method were 6.0% and 7.0%, respectively, and the limit of determination was 25 ng/ml. The CyG was analyzed by high performance liquid chromatography (HPLC), using a minor modification of the method described by Shibata et al. [29]. This assay had an intraassay coefficient varying from 3.1% to 7.0%. The interassay coefficient of variation was 7.2%. The limit of determination for this method was 20 ng/ml. In addition to cyclosporine trough level monitoring, frequent blood samples were taken during a 12-h dosage interval (0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h after the dose) at 3 and 6 months after transplantation for calculation of the area under the concentration-versus-time curves (AUC) of CyG and A and the mean concentrations during the steady state. The AUC was calculated by the linear trapezoidal method.

Sampling for routine blood chemistry, hematology, and urine analyses was performed daily during hospitalization; additional investigations were performed twice weekly and once weekly from the time of discharge to month 3, twice monthly during months 4–6, and once monthly thereafter. The kidney function was monitored by serial determinations of the serum creatinine levels and endogenous creatinine clearance. In addition, assessment of the glomerular filtration rate (GFR), using the chromium-ethylene diamine tetraacetic acid (EDTA) clearance method, was performed at 3 months after transplantation. When patients were switched from CyG to CyA, no further comparative evaluation of laboratory parameters was carried out.

Percutaneous transplant biopsies were performed at the time of transplantation and at 2–6 months after transplantation. All biopsies were fixed in 3% buffered formalin and embedded in paraffin by routine procedures. Sections were cut at 3 μm and stained with H & E, Ladewig's trichrome stain, and silver methenamine. Microscopy study of the biopsies was carried out without knowledge of the group to which the patient belonged. The relative volume (volume density) of the renal cortical interstitium was used as the main parameter for evaluating renal interstitial fibrosis, which is the usual finding in chronic cyclosporine nephrotoxicity [33]. In addition to this quantitative analysis, the following histological changes were semiquantitatively assessed on a 0–4 score scale: interstitial inflammation, arteriolar hyalinosis, arteriolar smooth muscle degeneration, arteriolar intimal swelling and thrombosis, arterial intimal fibrosis, arterial signs of chronic vascular rejection, and arterial signs of acute vascular rejection. The occurrence of glomerular changes and of significant interstitial edema was also recorded. The microscopical evaluation procedure has been described previously [38].

Biopsy data were analyzed by linear regression and one-way analysis of variance (ANOVA). For the difference between mean values, Student's *t*-test was used whenever applicable. A P value < 0.05 was considered to indicate a significant difference.

Results

Both preparations of cyclosporine were in general well tolerated. At the end of the follow-up period (1 year after transplantation), patient survival was 100% in both groups. In the CyG group one graft was lost 8 months after transplantation, due to rejection. In dhe CyA group one graft never functioned. When the graft was removed 1 month after transplantation, it showed severe signs of rejection. Thus, the graft survival was 80% in both groups at the end of the follow-up period.

Renal function, as expressed by the serum creatinine level and endogenous creatinine clearance, did not differ between the two groups during the first 2 months after transplantation (Table 2). Chromium-EDTA clearance at 3 months after transplantation did not differ between the CyG and the CyA groups (28.0 ± 10.6 ml/min and 28.3 ± 8.2 ml/min, respectively). Evaluation of the biopsy material showed no difference between the groups regarding fibrosis at the time of transplantation. In the follow-up biopsies, however, a statistically significant difference between the groups was found regarding the relative volume of the cortical interstitium. The mean interstitial volume was lower in the CyA-treated patients than in the CyG-treated group (33.5 ± 5.6 and 42.5 ± 3.4, respectively, $P < 0.05$) (Fig. 1). No statistically significant difference was found between any of the other parameters measured.

All patients in the study experienced at least one episode of rejection. The number of rejection episodes was 11 in the CyG group and 9 in the CyA group.

Two episodes of biopsy-verified acute cyclosporine nephrotoxicity were diagnosed in the CyA group and 1 in the CyG group.

Table 2. Blood chemistry results 2, 4, and 8 weeks after transplantation in the CyG- and in CyA-treated patients (reference limits for healthy subjects are given within parentheses)

	Two weeks		Four weeks		Eight weeks	
	CyG ($n=5$)	CyA ($n=4$)	CyG ($n=5$)	CyA ($n=4$)[a]	CyG ($n=3$)[b]	CyA ($n=4$)[a]
Creatinine clearance (ml/min) (85–145)	38.5 ± 4.9	44.7 ± 15.11	40.3 ± 7.0	36.3 ± 3.2	56.3 ± 6.7	37.7 ± 8.0
Serum creatinine (μmol/l) (< 120)	272.0 ± 110.7	179.8 ± 66.4	211.5 ± 32.2	289.8 ± 199.6	185.7 ± 14.2	178.0 ± 39.4
Serum urea (mmol/l) (3.0–7.5)	25.6 ± 11.3	12.5 ± 3.9	16.9 ± 5.8	23.3 ± 15.7	16.8 ± 3.0	15.4 ± 6.4
Serum bilirubin (μmol/l) (< 26)	30.8 ± 9.9	7.8 ± 1.6***	13.2 ± 4.2	13.7 ± 7.0	11.7 ± 4.9	9.7 ± 3.9
Serum ALAT (μkat/l)	1.6 ± 0.5	0.4 ± 0.3**	1.8 ± 1.9	0.3 ± 0.1	0.8 ± 0.7	0.3 ± 0.1
Serum ASAT (μkat/l) (< 0.7)	1.2 ± 0.7	0.3 ± 0.2*	0.6 ± 0.5	0.2 ± 0.1	0.4 ± 0.2	0.3 ± 0.1
Serum AP (μkat/l) (< 4.2)	2.6 ± 0.7	2.8 ± 1.1	4.0 ± 1.7	4.3 ± 0.9	3.4 ± 0.3	3.6 ± 1.0
Serum albumin (g/l) (35–46)	25.8 ± 2.1	27.3 ± 1.7	28.3 ± 5.1	29.3 ± 2.5	27.7 ± 2.9	31.0 ± 2.0
B-Hemoglobin (g/l) (115–165)	93.2 ± 17.2	90.6 ± 8.3	91.8 ± 15.4	95.8 ± 11.6	111.0 ± 11.1	119.8 ± 14.6

*** $P < 0.001$, ** $P < 0.005$, * $P < 0.02$

[a] One patient with a nonfunctioning graft posttransplant is excluded

[b] Two patients who switched to CyA therapy are excluded

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; AP, alkaline phosphatase

The doses of CyG and CyA administered are shown in Fig. 2. During the first 2 months the trough levels of cyclosporine were higher than recommended in both groups (Fig. 2). Although the doses were significantly ($P < 0.05$) lower in the CyG group during the first 5 weeks, the trough levels were higher in this group at 2 weeks after transplantation. The doses of azathioprine and prednisolone did not differ between the two groups. The CyG trough concentration/dose ratio was higher than that in CyA-treated patients (intraindividual mean

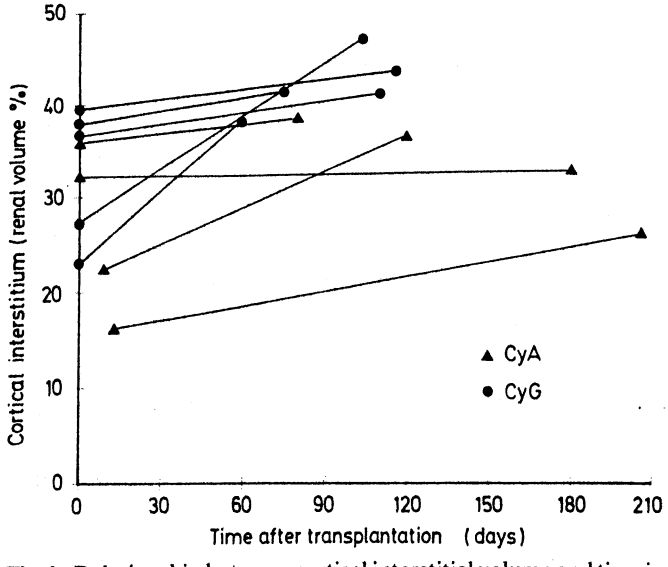

Fig. 1. Relationship between cortical interstitial volume and time interval between transplantation and biopsy in renal allograft biopsies from CyA- and CyG-treated patients with functioning grafts

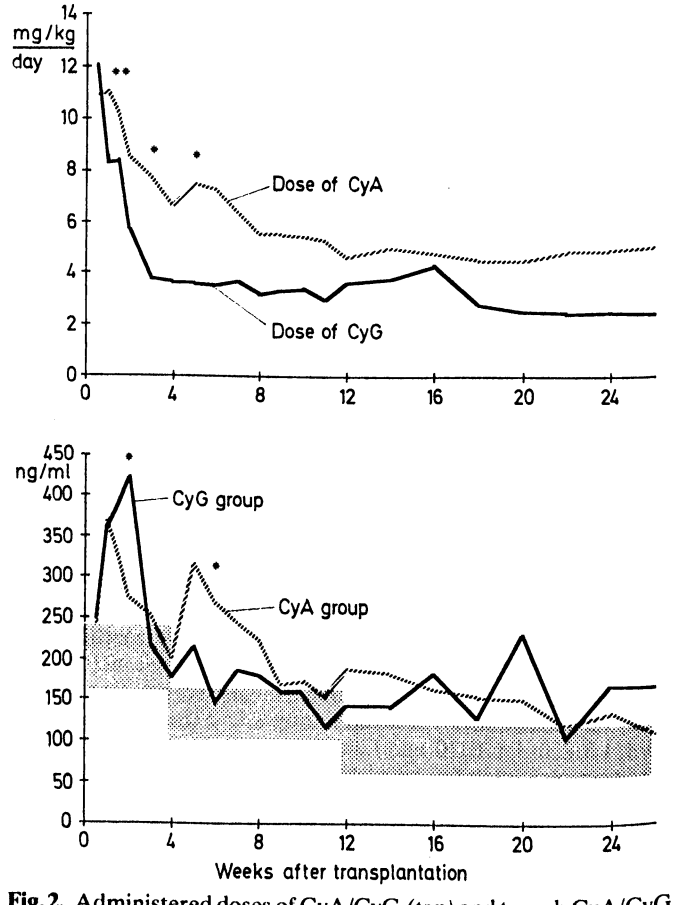

Fig. 2. Administered doses of CyA/CyG *(top)* and trough CyA/CyG concentrations *(bottom)*, mean values. *Asterisks* indicate significant differences: * $P < 0.05$, ** $P < 0.01$ (*shaded areas* indicate intended levels)

0.79 ± 0.23 ng/ml·mg versus 0.53 ± 0.11 ng/ml·mg in the respective groups between 14 and 80 days after transplantation; $P < 0.05$), which would suggest that there is a difference in the pharmacokinetics of the drugs. However, the dose-adjusted 12-h AUCs at 3 and 6 months after transplantation did not differ between the groups. At 3 months the dose-adjusted AUCs were 1152, 627, and 680 ng·h/ml·mg in the CyG-treated patients and 809, 398, 872, and 497 ng·h/ml·mg in the CyA-treated patients (n.s.). Furthermore, the dose-adjusted 12-h AUCs at 6 months after transplantation did not differ significantly from those at 3 months in either group.

Marked signs of hepatotoxicity were observed in all patients in the CyG group (Table 2). Serum bilirubin, alanine and aspartate aminotransferase (ALAT, ASAT) activities were significantly higher in the CyG group during the 1st month after transplantation, but the serum alkaline phosphatase activity did not differ between the two groups (Fig. 3). The pathological liver chemistry in the CyG group was reversible after reduction of the CyG dose in all but 1 patient. In that patient, the liver enzymes normalized after switching to CyA. One patient in the CyG group suffered from severe headache during the weeks following transplantation and was also icteric at that time. Apart from hepatotoxicity, all other blood chemistry and hematology parameters were in the normal range and did not differ between the two groups during the first 2 months following transplantation (Table 2). No other adverse effects were recorded.

As study end-point it was decided that patients in the CyG group who had more than one rejection episode should be switched to CyA. This was the case in 3 patients who were switched to CyA after 1.5, 2, and 4.5 months of treatment. Another patient was switched to CyA therapy 3 months posttransplant, at his own request. Shortly after this, one patient experienced an acute rejection episode that was successfully treated. The concentrations of CyG and CyA before and after changing the preparation were adequate in this patient. Otherwise, no alterations in graft function were observed after switching from CyG to CyA. The single patient who remained on the study drug at the end of the follow-up period (1 year after transplantation) was given CyA 16 months after transplantation because it was decided to terminate the study. Before and after this, the patient has been doing well, with good and stable graft function.

Discussion

The immunosuppressive potential of CyG compared with CyA has been a matter of debate. The initial reports by Hiestand et al. [18, 19] implied that the immunosuppressive potencies were equivalent in the rat model (skin, heart, and kidney grafts). These findings were later supported by Grant et al. [14]. An identical immunosuppressive efficacy after liver transplantation in dogs was also reported [34]. In a similar type of canine model, Calne et al. suggested that CyG was more effective than CyA, but in that study the concentrations of CyG were higher than those of CyA [5]. Studies in rats undergoing heart and lung transplantation, however, have suggested that CyG is less effective than CyA [28].

Conflicting reports have been presented regarding the pharmacological profile of CyG, as compared with that of CyA. Several groups have reported higher concentrations of CyG than of CyA when both drugs were given in equal doses. This finding was noted in both transplanted [5, 14, 34] and in nontransplanted animals [12, 16, 36]. It has been thought to be due to a lower clearance of CyG rather than to greater absorption from the gastrointestinal tract [15, 36]. However other studies indicate the attainment of equal CyG and CyA concentrations [7, 9, 17], or even lower concentrations of CyG [26], with equivalent dose administration. The general conclusion has been that there are both species [5] and strain [7, 9, 18, 19] differences in the absorption, metabolism, and excretion of the two cyclosporine analogues. Most of these analyses were performed with the polyclonal radioimmunoassay (RIA) method which gave a high cross-reactivity to drug metabolites. One possible explanation for the higher CyG levels found in most studies is that the CyG-induced hepatotoxicity reduces the clearance of metabolites and results in higher polyclonal RIA levels. Such an increased metabolite/parent compound ratio has been observed in CyA-treated patients with cholestasis or hepatic dysfunction after living transplantation [30, 39]. In a previous study in which CyG was administered to 6 nontransplanted patients with renal failure [37], the pharmacokinetics, as analysed by HPLC, were similar to those described for CyA in a corresponding patient population [13]. This finding suggests that the same dose strategies would apply for CyG use in man as those that have been established for CyA. In the present study, CyA and CyG levels were determined by specific monoclonal RIA and HPLC, respectively. Both of these levels were found to be higher than intended, in spite of the drug monitoring and frequent dose adjustments (Fig. 3). Furthermore, the concentration/dose ratio was somewhat higher for CyG than for CyA, although the AUCs in the two groups at one time did not differ. These data suggest that the pharmacokinetics of the two drugs may differ.

Hiestand and colleagues initially reported that CyG was neither nephrotoxic nor hepatotoxic in Wistar rats [18, 19]. In the same type of model, Faraci et al. [12] reported that CyG was less nephrotoxic than CyA, but more hepatotoxic. The lower nephrotoxicity in rats was also described by others [8, 16, 23]. In contrast, Duncan et al. [9, 10] reported that CyG shared the nephro- and hepatotoxic properties of CyA, at least in the high dose of 50 mg kg/bw per day, in Sprague-Dawley rats. By using a lower dose (25 mg kg/bw per day), Tejani et al. [32] observed less nephrotoxicity after CyG administration than after CyA in the same model. In the dog model, Calne et al. [5] suggested that CyG might be less nephrotoxic than CyA. Previous clinical experience is limited and consists of 12 patients who received CyG (initial dose 12 mg/kg daily) as primary therapy along with steroids for 3 months after transplantation [20]. The patients were then switched to other types of immunosuppression. The 1-year graft survival was 70%. In that study 6 patients showed clear signs of reversible hepatotoxicity. An addi-

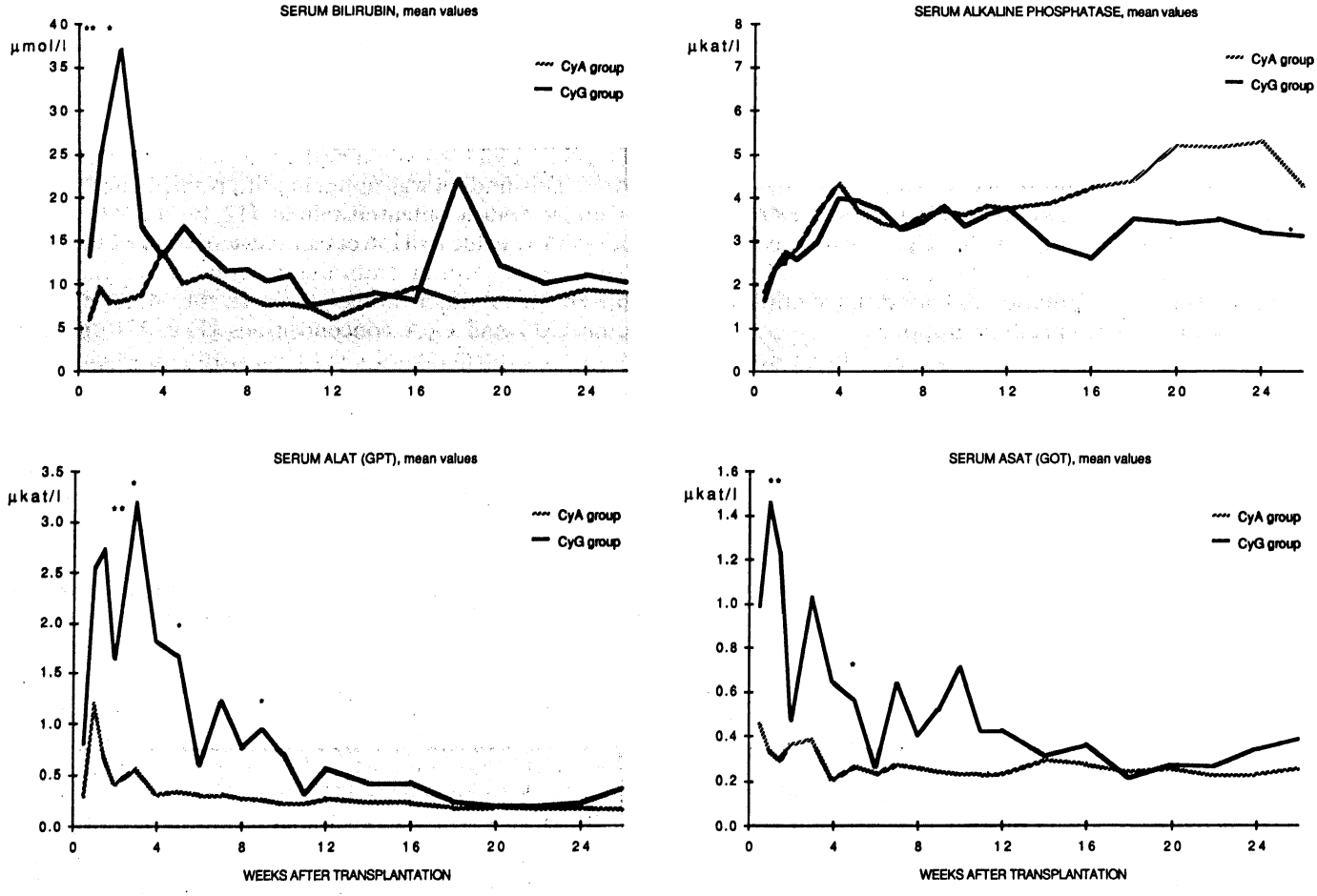

Fig. 3. The mean values of serum bilirubin, alkaline phosphatase, ALAT and ASAT in the CyA- and CyG-treated groups. *Asterisks* indicate significant differences: * $P < 0.05$, ** $P < 0.01$ (*shaded areas* indicate reference limits in healthy subjects)

tional 6 patients showed clear signs of reversible hepatotoxicity. An additional 6 patients with preexisting CyA-induced nephrotoxicity were converted to CyG for 6–12 months without any beneficial effect on renal function [1]. One of these patients experienced transient hyperbilirubinemia in conjunction with high whole blood CyG concentrations (1367 ng/ml, target concentration 250–600 ng/ml). In these studies the CyG doses were high and the CyG concentrations were much higher than intended.

In the present study we found that CyG like CyA can cause acute episodes of impaired renal function. The renal function, as expressed by laboratory parameters, did not differ between the two groups during the study period. In the follow-up biopsies we observed a significantly higher degree of fibrosis in the CyG group, but these data must be interpreted with caution because of the small number of patients. One must also take into account that 2 of the CyG patients had been switched to CyA 1 month prior to the follow-up biopsies. We found, however, that CyG was definitely more hepatotoxic than CyA. This hepatotoxicity was mainly observed during the first weeks after transplantation, when the dose given and the blood levels of CyG were highest. The pathological liver values normalized in all but 1 case when the dose of CyG was reduced.

In conclusion, we noted no clear advantages with the use of CyG as compared with CyA in renal transplantation. Its immunosuppressive properties were not superior to those of CyA, nor was there any indication that it was less nephrotoxic. CyG was, however, significantly more hepatotoxic than CyA. Our protocol allowed for the inclusion of more patients after the evalution of the first 10 patients. However, with the results obtained it was not thought justifiable to enter any additional patients.

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