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Cyclosporin A has no impact on alterations of the lipid profile after renal transplantation

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Abstract. The literature contains conflicting ideas regarding the role of cyclosporin A (CyA) in the induction of posttransplant dyslipidemia. The available studies contain small numbers of patients, especially on CyA monotherapy. We compared 65 patients on conventional azathioprine-prednisone therapy (AP) with 85 patients on CyA monotherapy, 19 on CyA-azathioprine therapy (CA), 20 on CyA-prednisone therapy (CP), and 52 on a triple therapy with CyA, azathioprine, and prednisone (CAP). From the results, it is concluded that patients on CyA monotherapy had lower serum cholesterol levels, with a lower high-density lipoprotein (HDL)-cholesterol level, probably due to the lower total cholesterol, compared with AP patients. From all groups, the CyA monotherapy group showed the most beneficial lipid profile. No additive negative influences of CyA when combined with other immunosuppressive drugs were noted. Thus, a correlation between derangements of the lipid profile and CyA therapy could not be confirmed. Further analysis of our data showed negative influences of antihypertensive treatment on lipid metabolism, particularly in the case of treatment with β-blockers or diuretics. It cannot be excluded that studies showing a negative influence of CyA therapy on lipid homeostasis were biased by secondary factors like antihypertensive therapy, which was often not taken into account.

Key words: Transplantation – Cyclosporin A – Lipids – Antihypertensive drugs – Insulin sensitivity – Immunosuppression

Modern immunosuppressive drugs, especially cyclosporin A (CyA), brought a radical improvement in the success rate of kidney transplantation. Graft survival after 1 year improved significantly [9–10]. The price paid for this progress is the well-known side-effects of CyA [14], e.g., hypertension, hypertrichosis, gingival hyperplasia, and possible disturbances in lipid metabolism [6, 13]. Hypertension and alterations in lipoprotein metabolism are among the major cardiovascular risk factors [3]. Almost 40% of renal recipient deaths are attributed to atherosclerotic cardiovascular disease [16].

Whereas prednisone negatively influences the lipid homeostasis [7], the role of CyA remains unclear. Most studies were carried out in small numbers of patients and are hampered by the fact that they were not controlled for blood pressure medication, a well-known cause of dyslipidemia [11]. Furthermore, there are no studies available with sufficient numbers of patients on CyA monotherapy. Most trials did not include lipoprotein analysis in their data, a necessary attribute to calculate the cardiovascular risk. A recent study demonstrated no harmful effect of CyA on cholesterol and triglyceride metabolism [12].

Since in the Renal Transplant Unit of Basle the ultimate goal is CyA monotherapy, we have the possibility to compare data derived from a large group of patients on CyA monotherapy with those on other immunosuppressive regimens.

Materials and methods

All patients that have undergone kidney transplantation come, apart from the usual follow-up, once a year for an intensive check-up to the transplantation center. As well as several clinical investigations, this includes blood samples taken in the morning after an overnight fast and before the morning dose of CyA for routine serum parameters and the estimation of the CyA level (parent drug level, monoclonal method, with normal range 75–200 ng/ml). On this occasion the lipid profiles are also analyzed: cholesterol and triglycerides by means of standard laboratory methods and the lipoproteins of cholesterol (high-density, low-density, and very low-density, HDL, LDL, and VLDL) by the ultracentrifuge method.

In all, 254 patients with stable renal function for at least 6 months and no change in medication for at least 6 months were enrolled in the study. Thirteen were excluded because of proteinuria exceeding 3 g/day or because they were on lipid-lowering drugs. Thus, 122 men and 119 women were available for the analysis. Data are expressed

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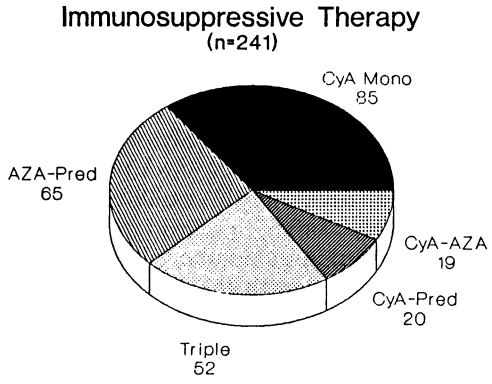

Fig. 1. Distribution of modalities of immunosuppressive therapy among the 241 patients included in the study

as medians since the underlying distribution of the data was not normal. Parameter-free testing by means of Wilcoxon and Mann-Whitney U-tests was applied.

Results

Five groups were created, depending on the modality of immunosuppression. The first one (n = 65) comprised all patients on the conventional combination therapy with azathioprine-prednisone (AP); the others were CyA monotherapy (n = 85) or combinations of CyA-prednisone (CP, n = 20), CyA-azathioprine (CA, n = 19), or triple therapy with CyA, azathioprine, and prednisone (CAP, n = 52) (Fig. 1).

The indications for the use of specific regimens will not be discussed here; it is worth mentioning that the CAP therapy was usually applied in the case of chronic rejection and that patients who were transplanted before the CyA era were maintained on their conventional therapy with AP if they had stable renal function.

As can be seen in Table 1, the AP group had the longest follow-up time, due to the aforementioned fact. There were no intergroup differences in age, body weight, and serum glucose level. If compared with the AP group, the serum creatinine level in the CP as well as in the CAP group was significantly higher, whereas the creatinine clearance was only significantly lower in the CAP group. This can be explained by the fact that the triple therapy group is the one which posed major problems due to chronic rejection before the institution of this therapeutic modality. Proteinuria was significantly lower in the CyA monotherapy group. Here we have a positive selection of patients who were easy to maintain on CyA monotherapy. Blood pressure was well regulated in all groups. The CyA monotherapy group showed a tendency towards a higher systolic blood pressure (142 mm Hg vs. 132 mm Hg in the AP group). The diastolic blood pressure was equal in all groups and amounted to 82 mm Hg (median).

In Fig. 2, the respective values of total cholesterol and triglycerides in all groups are given. Compared with the conventionally treated AP group, only patients with CyA monotherapy had a significantly lower serum cholesterol level. There were complicated differences regarding the cholesterol lipoproteins, as shown in Fig. 3. Again compared with the Ap group, the HDL-C level was lower (probably because the total cholesterol value was also lower in this group), and the VLDL-C value was significantly higher in the CyA monotherapy group. The responses in the other groups were heterogeneous, but especially the HDL value was significantly lower than under AP treatment, except for the CP group.

Next, the entire cohort was divided into a group on treatment with prednisone-containing regimens (n = 137) and one without prednisone (n = 104). In Table 2, the results are given. It appears that patients on regimens without prednisone had significantly lower serum cholesterol values and a concomitantly lower HDL-C value.

The influence of diuretics (almost exclusively loop diuretics) and β-blockers (in this case atenolol) was studied separately, and the results are given in Table 3. Diuretics aggravate the lipid disturbances and lower the HDL-C level; atenolol raises the serum cholesterol as well as the LDL-C level.

The cardiovascular risk coefficient, LDL/HDL-C showed no significant differences in the groups with or without prednisone treatment, but significant derangement in the groups on diuretics or β-blockers (Table 4).

Discussion

Since disturbances in the lipid metabolism probably have an important impact on cardiovascular mortality, especially in a vulnerable group like patients with a grafted kidney, more attention should be paid to preventing

Table 1. Nonlipidemic parameters in the 5 groups

	AP (n = 65)	CyA mono (n = 85)	CyA-P (n = 20)	CyA-A (n = 19)	Triple (n = 52)
Years since transplant	9	4	5	4	4
Age (years)	46	52	51	46	46
Body weight (kg)	68	70	67	65	71
Serum creatinine (μmol/l)	102	110	134*	114	169**
Creatinine clearance (ml/min)	71	64	55	53	42**
Serum glucose (mmol/l)	5.3	5.6	5.3	5.5	5.7
CyA plasma level (ng/ml)	–	124	153	95	85
Proteinuria (g/24 h)	0.26	0.17*	0.20	0.16	0.44

AP, azathioprine-prednisone; CyA, cyclosporin A
* $P < 0.005$, ** $P < 0.0005$ vs. Al group

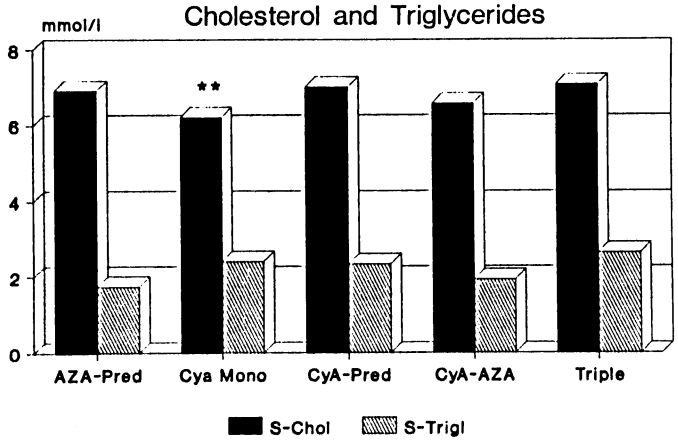

Fig. 2. Cholesterol and triglyceride values in the 5 different immunosuppressive regimen groups: $P < 0.01$ compared with conventional AP group

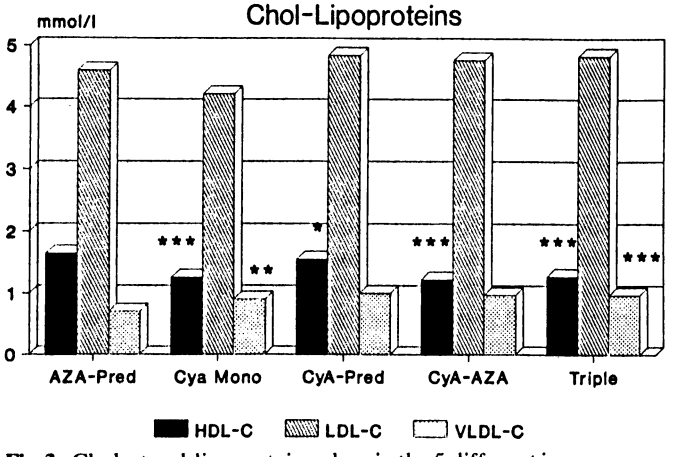

Fig. 3. Cholesterol-lipoprotein values in the 5 different immunosuppressive regimen groups: $P < 0.05$, $P < 0.01$, $P < 0.005$ compared with conventional AP group; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein

potential risk factors, e.g., drugs that promote dyslipidemia.

Although some studies have shown a negative impact of CyA therapy on these risk profiles, the methodology of these studies should be reviewed critically. The study by Ballantyne et al. [1] showed in 36 patients with amyotrophic lateral sclerosis an increase of 21 % in the serum cholesterol level in the CyA group compared with placebo. However, the follow-up lasted only 6 months, and a wide scattering of cholesterol values was found in this small group of patients. Furthermore, there was no correlation between the CyA drug levels and serum cholesterol.

Fuhrer and Horber [6] found an independent hypercholesterolemic influence of CyA and postulated that prednisone and CyA together may have an additive negative impact on the serum cholesterol level. This conclusion, however, is to be criticized because there were no patients on CyA monotherapy to be analyzed separately. Lipoproteins and antihypertensive drugs were not taken into account.

There are also studies demonstrating that CyA is not a potential dyslipidemic agent [2, 12]. These studies also had the problem that they did not include patients on CyA monotherapy to be analyzed separately.

The study by Hodel et al. [8], performed prospectively, compared 16 patients on AP with 17 on CyA monotherapy. After a follow-up of 13–28 months, no difference in the lipid profiles were found.

Our study is the first with a large number of patients on CyA monotherapy. Compared with the other immunosuppressive regimens, the patients on this therapeutic modality had even better lipid profiles.

The impression of Fuhrer and Horber [6] that CyA, if added to an immunosuppressive regimen, aggravates lipid disturbances could not be confirmed, since the results of combination therapy like CP, CA, or even CAP did not differ consequently from those of the AP therapy.

More important seems to be the role of antihypertensive treatment, since we found a remarkable negative impact of diuretics and β-blockers on cholesterol and its lipo-

Table 2. The influence of prednisone-containing regimens on lipid profiles (values expressed as medians in mmol/l)

	With prednisone (n = 137)	Without prednisone (n = 104)	P value
Serum cholesterol	6.83	6.23	< 0.005
Serum triglycerides	2.22	2.04	N.S.
HDL-C	1.35	1.20	< 0.005
LDL-C	4.63	4.28	N.S.
VLDL-C	0.76	0.77	N.S.

Table 3. The influence antihypertensive agents on lipid profiles (values expressed as medians in mmol/l)

	With antihypertensive	Without antihypertensive	P value
Diuretics	(n = 20)	(n = 54)	< 0.01
Serum cholesterol	6.21	6.02	< 0.05
Serum triglycerides	2.24	1.82	< 0.01
HDL-C	1.17	1.44	N.S.
LDL-C	4.13	3.73	N.S.
VLDL-C	0.77	0.75	
β-Blockers	(n = 29)	(n = 54)	
Serum-cholesterol	6.56	6.02	< 0.001
Serum-triglycerides	3.91	1.82	< 0.001
HDL-C	1.19	1.44	< 0.01
LDL-C	4.11	3.73	N.S.
VLDL-C	0.76	0.75	N.S.

Table 4. Cardiovascular risk factor LDL/HDL cholesterol coefficient

Therapy mode	n	LDL/HDL	P value
CyA monotherapy	85	3.32	
With prednisone	134	3.32	N.S.
Without prednisone	104	3.32	
Diuretic monotherapy	20	3.42	
No antihypertensive agents	54	2.53	< 0.001
β-Blocker monotherapy	29	3.14	
No antihypertensive agents	54	2.53	< 0.01

proteins. Probably, an altered insulin sensitivity is the cause of these derangements [5].

Although the same effect has been shown to be due to CyA medication [15], the impact of steroid treatment after renal transplantation is probably quantitatively more important [4].

In conclusion, CyA seems to be a 'safe drug' in respect to lipid metabolism and, hence, cardiovascular risk factors. More attention should be paid to the drugs chosen for the treatment of hypertension in these patients. Recent meta-analysis showed that diuretics and β-blockers should be avoided, whereas calcium channel blockers and angiotension converting enzyme inhibitors have a neutral effect on lipid metabolism and may become the drugs of first choice [11]. To confirm this impression, prospective studies including all immunosuppressive regimens are needed.

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