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Pronounced renal vasoconstriction and systemic hypertension in renal transplant patients treated with cyclosporin A versus FK 506

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Abstract This prospective study investigated hypertension and renal vasoconstriction developing during the 1st year after renal transplantation in patients randomly allocated to treatment with FK 506 ($n = 28$) or CyA ($n = 13$). Starting doses were 0.2–0.3 mg/kg per day for FK 506 and 5–8 mg/kg per day for CyA; doses were subsequently adjusted to trough levels (5–15 ng/ml for FK 506 and 100–150 ng/ml for CyA). We compared 24-h ambulatory blood pressure measurement, antihypertensive treatment, serum creatinine, and resistance index (RI), measured by Doppler ultrasound at the level of the interlobar artery. Until month 2 of treatment, FK 506-treated patients had a significantly lower RI (8 %) and better renal graft function, as evidenced by significantly lower serum creatinine values. Some 13 % of FK 506-treated patients, compared to 70 % of CyA-treated patients ($P < 0.01$), needed additional antihypertensive drugs after transplantation to keep blood pressure stable. FK 506 treatment, at the above-mentioned dosages, was associated with a significantly higher number of infections (urinary tract infection, pyelonephritis, and pneumonia). We conclude that CyA produces greater renal vasoconstriction and systemic hypertension than FK 506, as reflected in higher renal interlobar artery RI values and a greater need for antihypertensive treatment. After 2 months of treatment and a reduction in CyA trough levels, the renal effects (i.e., lower RI and lower creatinine values), but not the systemic hypertensive effects, disappear.

Key words Hypertension, immunosuppression, kidney · Kidney, hypertension, immunosuppression · Immunosuppression, kidney, hypertension

Introduction

In recent years, attempts have been made to compare the immunosuppressive actions, as well as the side effects, of the newly developed FK 506 (tacrolimus) with those of the well-established cyclosporin A (CyA) in renal transplantation. CyA is known to cause hypertension and nephrotoxicity, which is associated with renal vasoconstriction [10, 12]. Initial studies suggested that FK 506 was at least as effective as CyA-based regimens insofar as patient and graft survival were concerned [27–29, 32]. Immunosuppression seemed to be even more pronounced with FK 506-based regimens but, as a consequence, side effects, especially opportunistic infectious complications, were found to occur more frequently with this drug in our center [13]. Systemic hypertension is generally less severe with FK 506 than with CyA use, resulting in a lesser need for antihypertensive medication [2, 31]. Results with regard to renal vasoconstriction and associated nephrotoxicity are conflicting. Both reduced and unaltered renal vasoconstriction [2, 22, 31] have been reported with FK 506 after liv-

er and thoracic organ transplantation. However, no direct comparison of the renal and systemic hemodynamic effects of the two drugs has yet been performed. We therefore started a prospective, randomized trial in November 1993 to compare the renal and systemic hemodynamic effects of FK 506 and CyA-based regimens in renal transplantation.

Patients and methods

Between 3 November 1993 and 16 April 1994, 48 patients were entered into a randomized trial comparing FK 506/azathioprine/prednisolone and CyA-/azathioprine/prednisolone. Patients were randomized within 24 h after transplantation in a ratio of 2:1 to receive either FK 506 or CyA. The study was completed for a given patient either 12 months post-transplantation or if chronic rejection or intolerable toxicity was diagnosed; the patient was then withdrawn from the study. Seven patients were excluded, five in the FK 506 group and two in the CyA group, because the follow-up period was less than 9 months before withdrawal of the respective drug.

Inclusion criteria were: age 18 years or over; end-stage kidney disease and acceptance as a transplant candidate by the Hannover transplantation center; informed consent by the patient; a negative pregnancy test for females of childbearing age at screening and agreement to maintain effective birth control practice by female patients of childbearing age and male patients during the study and cadaveric kidney transplants only, without other organ transplants. Exclusion criteria were: significant liver disease; allergy or intolerance to CyA steroids, macrolide antibiotics, or FK 506; a kidney transplant from a donor with an incompatible ABO blood type; use of other study medications within the last 28 days; a positive T-cell crossmatch in the most recent recipient serum specimen; HIV-positive status (testing had to have been performed before randomization); and any previous non-kidney organ transplant.

The patient population was not selected and represented virtually all adults undergoing renal transplantation at the Medizinische Hochschule Hannover during this period. The study protocol was reviewed and approved by the Hannover Medical school ethics committee and was carried out in accordance with the ethical standards as set down in the 1964 Declaration of Helsinki.

Starting doses were 0.2–0.3 mg/kg per day for FK 506 and 5–8 mg/kg per day for CyA, each divided into two doses given p.o. every 12 h at 8:00 a.m. and 8:00 p.m. Doses were subsequently adjusted to trough levels, which were determined every morning at the same time before administration of the respective medication. Target trough levels were 150 ng/ml on days 1–89 and 100–150 ng/ml on days > 90 for CyA, and they were 10–20 ng/ml on days 1–89 and 5–15 ng/ml on days > 90 for FK 506. Trough levels were determined daily during the initial 3 weeks (clinical phase) and at monthly intervals thereafter. Doses were modified as deemed necessary to minimize adverse effects and to maintain effective immunosuppression. Doses for steroids and azathioprine were the same for all patients, i.e., steroids: methylprednisolone 500 mg intraoperatively and 125 mg 24 h after reperfusion given i.v.; prednisone: p.o. 20 mg on days 2–14, 15 mg on days 15–28, 10 mg on days 29–42, and 5 mg on days 43–365; azathioprine: 2 mg i.v. bolus 6 h after reperfusion and, starting on day 1, 1 mg/kg body weight (BW) p.o. with initial renal function and 2 mg/kg BW p.o. without initial renal function. Azathioprine treatment was reduced or stopped if the white blood cell count dropped below 4000/μl and it was discontinued after 90 days of treatment if clinically possible. FK 506 trough levels were determined by Abbot IMX [9] and CyA trough levels by a monoclonal specific RIA kit (Sandoz, Basel, Switzerland).

Table 1 Ranges of antihypertensive drug doses defined as low, intermediate, or high for calculation of dosage score

	Drug dosage range (mg/day)		
	Low (1)	Intermediate (2)	High (3)
Atenolol	< 25	25–50	> 50
Bisoprolol	< 5	5–10	> 10
Captopril	≤ 25	25–50	> 50
Carvedilol	< 25	25–50	> 50
Clonidine	< 150	150–450	> 450
Dihydralazine	≤ 25	50	> 50
Diltiazem	< 180	180–240	> 240
Doxazosine	< 3	3–6	> 6
Enalapril	≤ 5	> 5–10	> 10
Hydrochlorothiazide	< 25	25	25
Lisinopril	> 5	5–10	> 10
Methyldopa	< 500	500–750	> 750
Metoprolol	< 150	150–200	> 200
Moxonidine	≤ 0.2	0.2–0.3	> 0.3
Nifedipine	< 40	40–120	> 120
Nitrendipine	< 20	20–30	> 30
Verapamil	< 120	120–240	> 240
Urapidil	< 120	120–180	> 180

We compared 24 h ambulatory blood pressure measurements (spacelab) and antihypertensive treatment (AHT) during the 1st week after renal transplantation, at month 1 (days 8–60), month 3 (days 61–135), month 6 (days 136–270), and month 12 (days > 270). A semiquantitative score was derived for the antihypertensive drugs to allow a comparison of overall dosage across drug categories as follows [16]. For each drug, mean daily doses were graded as low, intermediate, high and were assigned the scores 1, 2, and 3, respectively; 50 ml/min was taken as the mean creatinine clearance (Table 2). The dosage score for each individual was the sum of the scores of all drugs taken.

The renal arterial resistance index (RI) was measured by Doppler ultrasound (mean of three measurements from the upper, middle and lower poles of the kidney) taken at the level of the interlobar artery [RI = 1-(minimum end diastolic velocity/maximum systolic velocity); Ultrasound scanner SSA 270 A, Toshiba, Tokyo]. RI measurements were taken daily during the first 21 days after transplantation (clinical phase), at monthly intervals until month 6 after transplantation (ambulatory phase), and at bimonthly intervals thereafter. All measurements were taken by the same investigator (M.M.) at the same time of day, 5:00–6:00 p.m. (9–10 h after ingestion of CyA and FK 506). Blood pressure, RI, and creatinine values that were determined during periods of histologically proven graft rejection, urinary tract obstruction with ultrasonographic evidence of dilated calyxes, or infectious episodes (urinary tract infection or pyelonephritis proven by urine culture, sepsis, or pneumonia) were omitted from further analysis.

Laboratory parameters evaluated included serum creatinine and serum sodium.

All data are reported as means ± SEM. Differences in the responses of FK 506 and CyA-treated patients were tested for statistical significance using the unpaired *t*-test for group differences. Differences in proportions were tested using Pearson's chi-square test of association. Correlations were assessed by linear regression

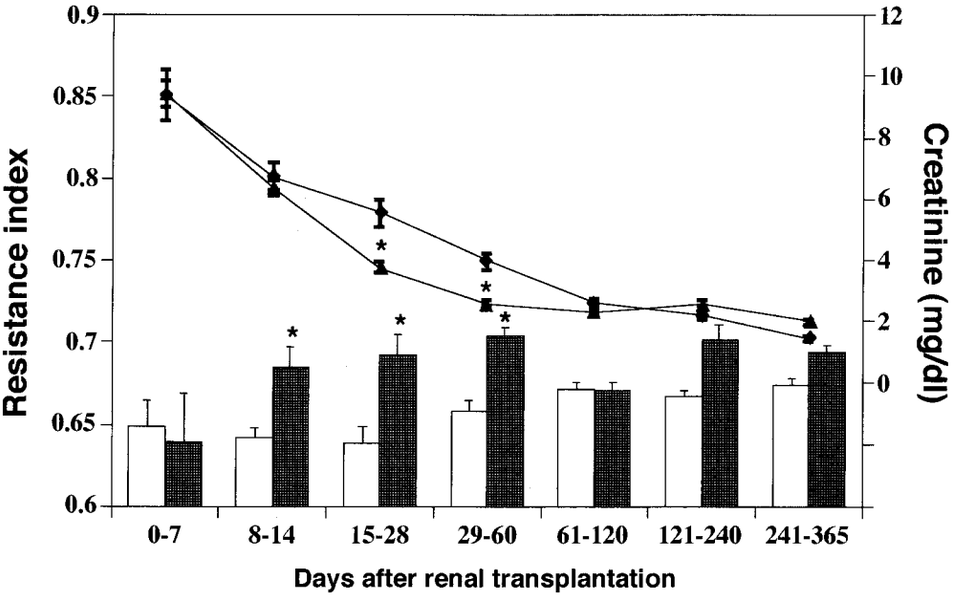

Fig. 1 Interlobar artery resistance index (*RI*, mean of three measurements) and serum creatinine levels during the 1st year after renal transplantation in CyA ($n = 13$) and FK 506 ($n = 28$)-treated patient groups. Pretransplant creatinine values were similar in both groups. Between days 14 and 61, creatinine and RI values were lower in FK 506-treated patients. Data are shown as mean ± SEM. *$P < 0.05$. Resistance index: □ FK 506; ▦ CyA; Creatinine: —▲— FK 506; —◆— GyA

analysis. When multiple comparisons were made a repeated measures analysis of variance (Scheffe's test) was performed. Significance was accepted at the 0.05 level of probability.

Results

Patient characteristics are shown in Table 2. There were no significant differences between the two groups. Five patients in the FK 506 group and two patients in the CyA group had to be excluded because the follow-up period before withdrawal of the respective drug was less than 9 months. These patients were excluded for the following reasons: FK 506 group: unstable angina pectoris ($n = 1$), persistent transplant nonfunction ($n = 1$), severe infection (pneumonia; $n = 2$), and diabetes mellitus requiring insulin treatment ($n = 1$); CyA group: transplant renal vein thrombosis ($n = 1$) and chronic rejection ($n = 1$). The mean follow-up for the remaining patients was 363 ± 19 days for the FK 506 and 367 ± 13 days for the CyA-treated patients.

The RI in interlobar renal arteries was significantly higher in CyA-treated patients from day 8 until about day 60; thereafter, the difference was no longer significant (Fig. 1). During this time, serum creatinine values were also higher in CyA-treated patients, with values reaching significance between days 15 and 60. There was a weak, but significant, correlation of RI values and serum creatinine in CyA-treated ($r = 0.26$, $P = 0.0003$), but not in FK 506-treated patients, until day 60; thereafter, no significant difference could be observed in either group. Higher creatinine values in the CyA group during this time were not due to concomitant drug use (cefoxitin, cephalothin, trimethoprim, flucytosine, methyldopa, cimetidine) since no statistical significance in the use of these drugs between the two treatment groups was observed during this time. RI values increased during episodes of rejection in both FK 506 and CyA-treated patients, but the difference was significant in the FK 506-treated patients only (Fig. 2), possibly due to higher basal RI values in CyA-treated patients obscuring the effect of rejection. Urinary tract obstruction, as evidenced by pelvocaliectasis,

Table 2 Patient characteristics (mean ± SEM)

	FK 506	CyA	*P*
N	28	13	
Age	41.3 ± 2.3	47.1 ± 3.5	NS
Sex (% male)	63	50	NS
Size (cm)	171 ± 2	169 + 2.5	NS
Body weight (kg)	66.8 + 2.2	71.2 + 2.7	NS
Time on dialysis (years)	4.3 + 0.7	5.2 + 0.9	NS
Urinary volume pre-Tx (ml)	192 + 63	258 + 88	NS
Hypertension pre-Tx (%)	19/32 (59%)	7/14 (50%)	NS
HLA(A) match (x/2)	0.81 + 0.12	0.85 + 0.22	NS
HLA(B) match (x/2)	0.89 + 0.12	0.77 + 0.23	NS
HLA (DR) match (x/2)	0.35 + 0.09	0.39 + 0.14	NS
Antibody (%)	4.2 + 1.9	3.1 + 1.8	NS
Previous transplants	0, $n = 25$ 1, $n = 2$ 2, $n = 1$	0, $n = 11$ 1, $n = 2$ 2, $n = 0$	
Cold ischemic time (hours)	22 ± 7	24 ± 8	NS

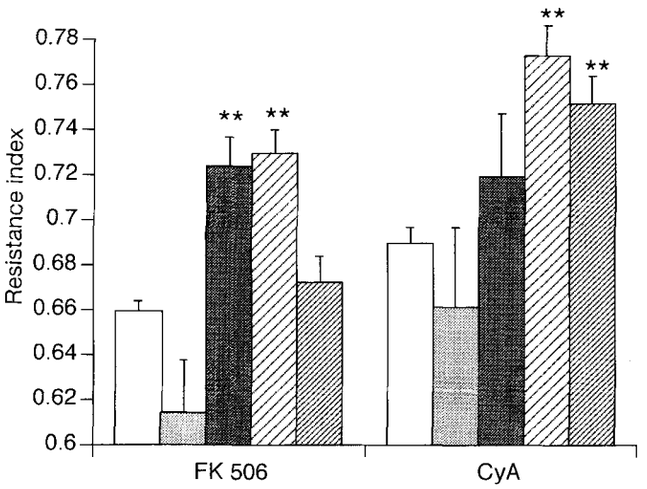

Fig. 2 Interlobar artery resistance index (RI, mean of three measurements at three different locations) in different clinical states. Rejection episodes were associated with an increase in RI; however, the difference was significant in FK 506-treated patients only. Pelvocalicectasis increased RI in both treatment groups, whereas initial dysfunction was associated with increased RI values in CyA-treated patients only. Data are shown as mean ± SEM. $^{**}P < 0.01$. ☐ No clinical problem; ▦ before rejection; ▩ acute rejection; ▨ pyelektasia; ▨ initial dysfunction

Table 3 Mean 24-hour blood pressure data

		Day 1–210	Day > 210
Mean systolic BP (mm Hg)	FK 506	135 ± 2	132 ± 3
	CyA	134 ± 2	132 ± 3
Mean diastolic BP (mm Hg)	FK 506	81 ± 1	80 ± 2
	CyA	81 ± 2	81 ± 2
Highest systolic BP (mm Hg)	FK 506	166 ± 3	170 ± 5
	CyA	163 ± 3	164 ± 6
Highest diastolic BP (mm Hg)	FK 506	109 ± 2	107 ± 4
	CyA	109 ± 3	114 ± 6
Systolic > 140 mm Hg (%)	FK 506	35.3 ± 3.7	29.9 ± 6.4
	CyA	36.7 ± 5.6	32.4 ± 7.6
Diastolic > 90 mm Hg (%)	FK 506	23.8 ± 3.3	20.2 ± 5.4
	CyA	22.2 ± 3.9	21.2 ± 5.5

was associated with increased RI in both groups, whereas initial dysfunction was associated with increased RI in CyA-treated patients only.

There were no significant differences between the FK 506 and CyA-treated patients in any of the parameters that could be evaluated by 24-h ambulatory blood pressure measurements (Fig. 3, Table 3). However, the antihypertensive score (Fig. 3), which was initially significantly lower in the CyA-treated patients, increased fourfold during the course of the study (0.88 ± 0.40 vs 3.46 ± 0.51) and was significantly higher in these patients than in the FK 506-treated patients at the end of the investigation period. Some 13 % of FK 506 treated patients, compared to 70 % of CyA-treated patients, needed more antihypertensive drugs within the 1st year after transplantation to keep blood pressure stable ($P < 0.01$). Serum sodium levels were significantly lower in the FK 506-treated patients (Table 4).

FK 506 treatment was associated with a lower incidence of initial graft nonfunction and a lower rate of acute, biopsy-proven rejection (Table 5); however, these differences did not reach statistical significance, possibly due to the small sample size. As for additional immunosuppressive drugs, almost identical amounts of steroids were given to both groups of patients (FK 506 vs CyA: 14.2 ± 0.2 vs 14.7 ± 0.3 mg/day on days 1–210 and 6.2 ± 0.4 vs 6.0 ± 0.2 mg/day on days > 210) while azathioprine, which was initially given to all patients (FK 506 vs CyA: 1.53 ± 0.03 vs 1.54 ± 0.04 mg/kg per day), was discontinued in 3 of 13 CyA and in 26 of 30 FK 506-treated patients ($P < 0.01$). Infectious complications (Table 6) occurred more frequently in FK 506-treated than CyA-treated patients within the 1st year after renal transplantation.

Discussion

FK 506 treatment was associated with lower RI and creatinine values during the first 2 months of treatment and with a persistently lower need for additional antihypertensive treatment following renal transplantation than was CyA. This suggests that CyA has a higher renal vasoconstrictive potential and an increased tendency to cause hypertension than FK 506.

The RI accurately reflects renal vascular impedance in the vascular bed distal to the measured artery [3]. Increased vascular resistance is generally associated with reduced renal graft function but is by no means specific for morphological lesions and does not reflect disease severity [14, 21]. Renal RI has been shown to rise in all cases where peripheral vascular resistance is increased due to narrowing of peripheral arteries, either by direct vasoconstriction or indirectly when renal parenchyma are compressed. Clinical situations in which RI is increased include renal graft rejection [5, 20], acute tubular necrosis [25], urinary tract obstruction [7, 33], and a heavyhanded investigator compressing the kidney himself.

In our study, after exclusion of all criteria that might have influenced the RI (graft rejection, urinary tract obstruction, acute tubular necrosis), CyA treatment was still associated with significantly higher RI values at the level of transplant renal interlobar arteries up to 60 days after renal transplantation as than FK 506. Since the FK 506 group had a greater need for antihypertensive treatment already at the onset of the study, it could be argued that the lower RI in this group was due to

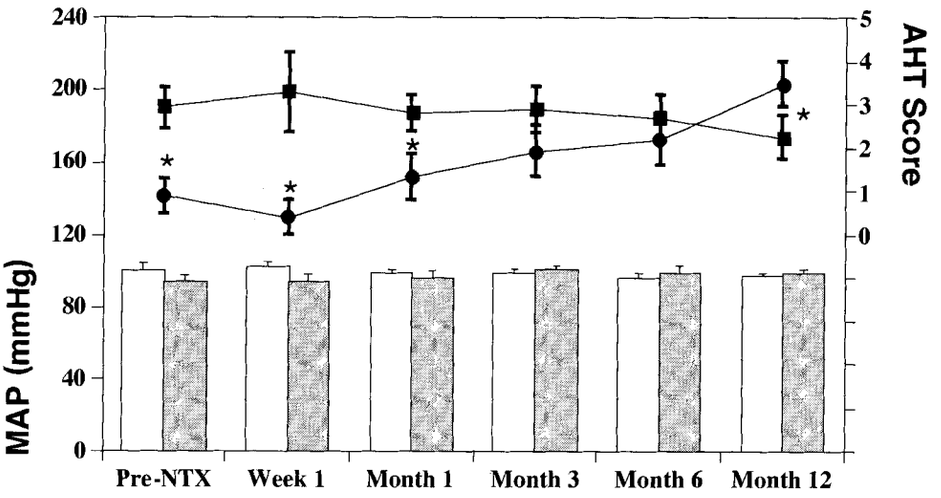

Fig. 3 Mean arterial pressure (*MAP*) of 24 h ambulatory blood pressure recording and antihypertensive drug score (*AHT*) during the 1st year after renal transplantation in CyA ($n = 13$) and FK 506 ($n = 28$)-treated patient groups. MAP was never significantly different between the two treatment groups, whereas AHT-score, which was significantly lower in CyA-treated patients at the start of renal transplantation, increased with time and was significantly higher in CyA-treated patients at the end of the study period. Data are shown as mean ± SEM. *$P < 0.05$. □ FK 506; ▨ CyA; —■— FK 506; —●— CyA

Table 4 Laboratory values under treatment with FK 506 and CyA

		Pre-NTX	Day 1–210	Day > 210
Blood levels (ng/ml)	FK 506	0	12.5 ± 0.2	8.2 ± 0.4**
	CyA	0	138 ± 4	98 ± 6**
Drug amount (mg/kg per day)	FK 506	0	0.225 ± 0.004	0.102 ± 0.009**
	CyA	0	4.66 ± 0.07	3.13 ± 0.14**
Creatinine (serum) (mg/dl)	FK 506	9.4 ± 0.4	3.3 ± 0.1	2.1 ± 0.1**
	CyA	9.5 ± 0.9	4.1 ± 0.2*	1.6 ± 0.1**
Urea (serum) (mmol/l)	FK 506	19.0 ± 1.5	16.2 ± 0.3	17.0 ± 2.5
	CyA	19.1 ± 2.1	17.7 ± 0.8*	14.4 ± 1.4
Sodium (serum) (mmol/l)	FK 506	140.7 ± 0.6	140.0 ± 0.3	138.6 ± 0.6
	CyA	140.9 ± 0.7	142.0 ± 0.7**	141.4 ± 0.4**

*$P < 0.05$; * $P < 0.01$ CyA vs FK 506; ** $P < 0.01$ day > 210 vs day 1–210

the use of antihypertensive drugs, which have been shown to be able to lower peripheral resistance [11]. However, before the start of treatment, when antihypertensive drug use was already significantly different between the two groups, the RI was not, and increasing the amount of antihypertensive drugs in the CyA group did not lead to a parallel decrease in the RI in this group (Fig. 1). The higher RI values in the CyA group were paralleled by higher serum creatinine values. An association between renal vasoconstriction and increased creatinine levels is suggested by the significant correlation of RI and serum creatinine observed in CyA-treated patients during this time. After day 60, the difference in RI values was no longer significant, and creatinine levels tended to be even lower in CyA-treated patients in association with a significant decline in CyA doses and trough levels.

Others have reported different effects of FK 506 treatment, namely, an increase in renal vascular resistance in both FK 506 and CyA-treated patients after liver transplantation [31] and higher serum creatinine values with FK 506 in the early post-transplant period after cardiac transplantation [2]. The discrepancy between our data and those findings in nonrenal transplant recipients may either reflect the lower rate of initial renal graft dysfunction with FK 506 treatment or be due to renal vasoconstrictive effects of FK 506 if these were mediated largely by renal nerves that are nonfunctional after renal transplantation. Such changes in adrenergic nerve traffic and sensitivity have been described with CyA [26]. Interestingly, RI values were increased during initial graft dysfunction in CyA-treated patients only, suggesting that the renal vasoconstriction may have been a cause of initial graft dysfunction in CyA but not in FK 506-treated patients. The frequency of initial graft dysfunction was also moderately higher in CyA-treated patients.

As for systemic hypertensive effects, FK 506-treated patients had a significantly lower demand for additional antihypertensive treatment. The initial report on the use of FK 506 in renal transplantation by Starzl et al. also reported a low incidence of post-transplant hypertension in an uncontrolled study [29]. Textor et al. reported a similarly reduced incidence of clinical hypertension (FK 506 vs CyA: 28 % vs 78 %) in liver transplant recipients in the first 4 months after transplantation [31]. The

Table 5 Rejection, antirejection treatment, and initial dysfunction with FK 506 and CyA treatment. Clinically suspected rejection was always confirmed by renal biopsy. Initial dysfunction is defined as urine production but no adequate drop in creatinine, leading to a further requirement of hemodialysis treatment for a variable period of time

	FK 506	CyA	*P*
Biopsy-proven rejection	11/33 (33 %)	8/15 (53 %)	NS
Antirejection treatment (mg methylprednisolone/ patient)	1583 ± 121	1563 ± 175	NS
Initial dysfunction and nonfunction	15/33 (45 %)	9/13 (60 %)	NS

Table 6 Infectious complications in FK 506 and CyA-treated patients (*CMV* cytomegalovirus, *EBV* Epstein-Barr virus, *HZV* Herpes-Zoster virus)

Episodes of	FK 506	CyA	*P*
Urinary tract infection[a]	48/33	15/15	< 0.05
Pyelonephritis	8/33	0/15	< 0.05
Pneumonia	7/33	0/15	< 0.05
Viral infection (CMV, EBV, HZV)[b]	4/33	1/15	NS

[a] Episodes of $> 10^5$ bacteria/ml of urine during the study period (1 year)

[b] Evidenced by a significant rise in virus antibody titers or evidence of virus IgM or electron microscopic evidence of urinary viral particles or a positive test for pp65 to detect CMV infection

reduced systemic hypertensive effect of FK 506 treatment was observed in the presence of relatively high levels of FK 506. FK 506 treatment was also associated with a moderately lower rate of biopsy-proven rejections than the CyA-based regimen.

The mechanism responsible for FK 506's lower systemic hypertensive potential in the long term and lower renal vasoconstrictive potential in the short term remains unclear. From our data it could be inferred that CyA causes hypernatremia or that FK 506 causes hyponatremia, as reflected in a higher serum sodium concentration in the CyA group. We cannot say which mechanisms caused this alteration in sodium balance because we did not routinely measure daily electrolyte excretion. Sodium retention has previously been stated as a cause of CyA-induced hypertension [4, 17]; however, up until now, no such effect has been described for FK 506. Different effects of FK 506 and CyA on nitric oxide inhibition may provide another explanation. FK 506 has been shown to cause a lesser reduction [1], or no reduction [15], of stimulated nitric oxide-production than CyA in rat smooth muscle cells. Nitric oxide is continuously released by endothelial cells and controls resting vascular tone. Thus, a reduced production would result in vasoconstriction. However, a variety of other factors involved in post-transplant hypertension under CyA treatment may also be responsible for the lower vasoconstrictive potential of FK 506. These include changes in adrenergic nerve traffic and sensitivity during CyA administration [26], changes in the balance of vasodilator/vasoconstrictor prostaglandins [6, 18], and the release of potent vasoconstrictor substances, such as endothelin [19], or vasodilator substances such as prostanoids [8, 24, 30]. Just which mechanism is responsible cannot be determined from the present data.

Although FK 506 treatment after renal transplantation is associated with a reduced renal and systemic vasoconstrictor potential and, possibly, a lower incidence of rejection episodes, at least in the dosages applied, it does not seem superior to conventional CyA treatment due to the higher frequency of severe infectious side effects (Table 6). CyA-treated patients had the expected rate of infectious complications. Although 15 urinary tract infections in 15 patients during the 1st year of treatment may seem high, an incidence of 50 % during the first 3 months with a later decline is the reported rate [23]. An optimal immunosuppressive regimen would have to combine lesser vasoconstriction than with conventional CyA treatment with an acceptable side effect profile and low rejection rates. Possible ways to achieve this could be to reduce the FK 506 dose or to combine lower CyA doses with additional immunosuppressive drugs.

In conclusion, CyA seems to cause more hypertension than FK 506, as reflected in the higher use of antihypertensive drugs, and FK 506 seems to cause less renal vasoconstriction in the initial post-transplant phase, as reflected in lower renal interlobar artery RI values and lower serum creatinine levels. Renal vasoconstriction, which is induced by the high initial doses of CyA and which leads to functional impairment, can be avoided with FK 506. After 2 months of treatment, the renal effects (i.e., lower RI and creatinine values) disappear as a result of reduced CyA trough levels. Neverless, the lesser systemic vasoconstrictive effect with the lower demand for antihypertensive drugs persisted even after 12 months of FK 506 treatment.

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