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Renal Transplantation in Baboons Under FK 506

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BEFORE embarking on a clinical trial of FK 506, the effectiveness and safety of this agent were examined with exhaustive animal studies in rats, dogs, and subhuman primates. Reported here are the results of baboon experiments, with renal transplantation and correlation with parallel *in vitro* mixed lymphocyte reaction (MLR) determinations. Part of this work was previously reported elsewhere.^{1,2}

MATERIALS AND METHODS

Unrelated female baboons, weighing 8 to 14 kg, were used. Renal transplantation was performed intraabdominally. Ureteroneocystostomy was made following removal of the native kidneys of the recipients. Lymphocyte sensitivity to FK 506 in rats, dogs, and baboons was determined using the one-way MLR, which is standard in our laboratories.²

RESULTS

Dose-Dependent Study

Starting on day 4, the baboons were given oral FK 506 in doses of 0 mg/kg/d (*n* = 4), 2 mg/kg/d (*n* = 2), 6 mg/kg/d (*n* = 4), 12 mg/kg/d (*n* = 5), and 18 mg/kg/d (*n* = 5). In addition, FK 506 was given to animals intramuscularly for the first 3 days. The oral medication was continued for 90 days. Using 90 days as a ceiling for calculation, the mean animal survival was 9.2 ± 4.0 (SD) days at 0 mg/kg/d, 16 ± 2.0 days at 2 mg/kg/d, 29.5 ± 21.2 days at 6 mg/kg/d, 70.8 ± 27.6 days at 12 mg/kg/d, and 74.6 ± 28.9 days at 18 mg/kg/d (Fig 1). Five animals receiving 12 or 18 mg/kg FK 506 lived for more than 90 days.

Graft Function and Pathology of Allograft

Renal failure developed rapidly in baboons receiving no FK 506 treatment, while those given FK 506 showed

dose-dependent maintenance of graft function. Histopathologic analyses of renal allografts in baboons who died within 90 days showed moderate to severe rejection, with the exception of two animals who died of pyelonephritis and unknown causes.

Hepatic Function and Blood Glucose

Hepatic function and blood glucose levels were normal and not significantly different in untreated and treated animals (Table 1).

FK Blood Levels

Blood levels were determined by an enzyme immunoassay using monoclonal antibody to FK 506.³ Although the doses given to animals varied between groups, there was no statistical difference in the blood levels (Table 1).

Histopathology of Extrarenal Organs

Specimens were collected at autopsy from 15 animals that died within 90 days. In five other baboons, a biopsy of the graft was performed at 90 days; these biopsies showed no important abnormalities in the liver and pancreas that were suggestive of drug side effect. There was no arteritis in any organs from any of the animals except for fibrinoid change of a single vessel in the appendix and the stomach.

Long-term Observations After Discontinuing FK Treatment

Of five animals who lived for more than 90 days after stopping oral FK treatment, four subsequently developed allograft rejection. A 3-day course of intramuscular FK 506 treatment, 2 mg/kg/d, reversed rejection in two of these four animals, but was not effective with the other two. All four animals died eventually of organ rejection. The fifth animal, which never had a rejection, was killed at 242 days, in a healthy state and at a time when renal function was normal. There was no histologic abnormality in the kidney or other organs.

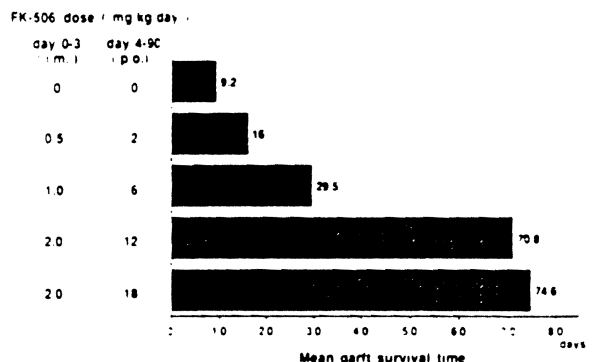


Fig 1. Mean survival of baboons treated with different doses of FK 506 after renal transplantation.

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Table 1. Postoperative SGOT, SGPT, Total Bilirubin, Blood Glucose, and FK 506 Levels in Baboons in Groups 1 to 5

Group	Dose of Oral FK 506 (mg kg d)	No.	SGOT (U/l)	SGPT (U/l)	Serum Total Bilirubin (mg dl)	Blood Glucose (mg dl)	Plasma FK 506 (ng/ml)
1	0	4	49.5 ± 49.5	12.0 ± 13.7	0.7 ± 0.4	103 ± 4	—
2	2	2	38.7 ± 19.7	37.4 ± 40.5	0.5 ± 0.5	87 ± 78	1.26 ± 1.20
3	6	4	45.0 ± 20.3	25.4 ± 17.6	0.4 ± 0.4	104 ± 20	4.27 ± 2.87
4	12	5	51.0 ± 28.8	29.7 ± 28.6	0.2 ± 0.2	86 ± 76	3.26 ± 1.85
5	18	5	49.4 ± 30.9	36.4 ± 64.6	0.4 ± 0.8	102 ± 43	5.24 ± 5.00

Sensitivity of Baboon Lymphocytes to FK 506

In the early stage of the baboon experiments, immunosuppression by FK 506 was unsuccessful, even when much higher doses than those given in earlier canine experiments⁴ were used. From this finding arose the question as to whether there was a difference in the sensitivity of lymphocytes to this agent between species. The results with MLRs under different concentrations in the medium show that cells from the baboon need a dose of FK 506 10 times higher than that needed by dogs or humans to suppress the MLR reaction (Table 2). This information is being reported separately.²

DISCUSSION

Our greatest concern was the potential toxicity of FK 506, which has previously been reported to cause diabetes,

lassitude, arteritis, and other serious problems in baboons.⁵ However, none of these major toxicities was seen in our baboon experiments, even when the FK 506 dose given daily over a 3-month period was 10 times higher than the dose causing lethal emaciation in dogs.⁴

The unexpectedly high dose required for prevention of allograft rejection in baboons correlated with the relative resistance of baboon lymphocytes to this drug, as shown with MLR testing. In addition, the *in vitro* experiments showed that human lymphocyte sensitivity was closer to that of dogs, a finding that was confirmed in our clinical experience.⁶ Therefore, FK 506 was a safe and effective immunosuppressive agent for renal transplantation in baboons. These experiments were performed in preparation for a clinical trial.

Table 2. Species Differences in the Sensitivity of Lymphocytes to FK 506

	FK 506 Concentration to Achieve a 50% Inhibition of MLR (ng/ml)	Optional Oral Dose (mg kg d)
Rat	0.33 ± 0.2	1-2
Dog	0.59 ± 0.58	1-1.5
Baboon	3.85 ± 2.0	12-18
Human	0.29 ± 0.2	0.15-0.3

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