Rapamycin in Experimental Renal Allografts in Primates

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We have reported[1] that rapamycin, a lipophylic macrolide antifungal antibiotic, produced by *Streptomyces hydroscopicus*, prolongs survival of rat cardiac allografts in a dose-dependent fashion. In the pig renal allograft model, a state of operational tolerance was achieved in three of nine animals after dosing at 2 mg/kg for up to 64 days following transplantation, and the five remaining animals died of the effects of overimmunosuppression with functioning grafts. In dogs receiving rapamycin, vomiting and bloody diarrhea associated with ulceration of the gastrointestinal tract and thrombocytopenia occurred at doses from 5 to 0.25 mg/kg per day. Histological examination of the ulcers showed an underlying necrotising fibrinoid vasculitis of arterioles and small arteries similar to that seen in dogs receiving FK 506.

MATERIALS AND METHODS

Renal allografts were performed between nephrectomised young outbred baboons with a negative crossmatch selected into pairs on the basis of histoincompatibility, using mixed lymphocyte reactions.

Dosing Schedule

Controls (n = 3). No drug administered.

Group 1 (n = 4). Rapamycin was given 2 mg/kg orally days −1 through 9.

Group 2 (n = 3). Four hundred sixty-four received rapamycin orally 2 mg/kg days −1 to 6, then 2 mg/kg intramuscularly days 7 to 13, 1 mg/kg days 14 to 15, 0.5 mg/kg days 16 to 19; 739 received rapamycin orally 50 mg/kg days 0 to 5, 5 mg/kg days 6 to 7, then intravenously 1 mg/kg days 12 to 15, 17 to 12; 526 received rapamycin intravenously 2 mg/kg days 0 to 7, 1 mg/kg days 8 to 11, 0.5 mg/kg days 12 to 17.

Group 3 (n = 3). Rapamycin given intravenously 1 mg/kg days 0 to 1, then orally either 25 or 10 mg/kg on alternate days, with individualised dose modifications.

RESULTS

In all animals, loss of appetite for formulated diet was noted, together with intermittent episodes of vomiting and

Table 1. Survival of and Histological Findings in Baboons Receiving Rapamycin Following Renal Allografting

Group	Survival in Days
Controls	8, 9, 11
1	6*, 7,* 9,† 9†
2	25*, 18,†‡ 25‡
3	32,*† 36,*† 40*†

*Rejection.
†Vasculitis.
‡Granulomatous infection.

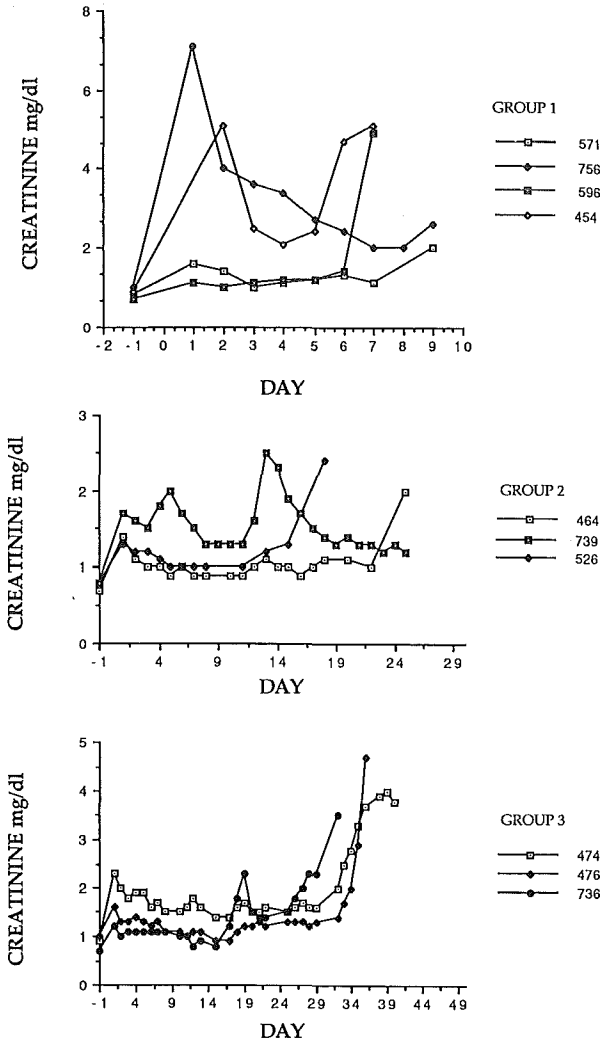

Fig 1. Serum creatinine of baboons given rapamycin after renal allografting.

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diarrhea. The survival of animals is shown in Table 1 and the serum creatinine in Fig 1. In group 1, two animals developed severe rejection in a time similar to that found in controls. The remaining animal was killed because of severe vomiting and collapse, had moderate focal rejection and fibrinoid vasculitis affecting the gut. In group 2, two animals were killed because they became lethargic and unwell, both had granulomatous infection but no rejection; however, one had a vasculitis affecting the gut. The third animal developed very painful injection sites, dosing was withdrawn, and death from rejection occurred. In group 3, all three animals showed evidence of toxicity with lethargy, vomiting, and diarrhea, and even a small dose reduction of 1 mg/kg lead to irreversible rejection; all showed evidence of vasculitis affecting the gut.

DISCUSSION

The results of the pig are encouraging—in three animals, a state of operational tolerance appeared to develop, furthermore, rapamycin seemed effective in the rat with few side effects. Rapamycin was immunosuppressive in the baboon, but the development of vasculitis in the baboon, similar to that seen in the dog, is of concern as this phenomenon can no longer be described as species specific. Further toxicology and the development of an assay must precede clinical trials.

REFERENCE

1. Calne RY, Collier DS, Lim S, et al: Lancet ii:227, 1989