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FK 506 Dosage In Human Organ Transplantation

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FK 506 has proved to be a new potent immunosuppressive drug in the initial clinical trials, which began at the University Hospital in Pittsburgh in February 1989.[1] FK 506 has been used as either primary immunosuppressant for liver, kidney, heart, lung, and heart/lung transplants, or as rescue therapy for liver or kidney transplants.

FK 506 is a macrolide derived from *Streptomyces tsukubaensis*. FK 506 suppresses T-cell-mediated immunity by suppressing interleukin-2 synthesis in T cells.[2]

The optimal dose of FK 506 in animals to achieve immunosuppression varies from 1-2 mg/kg in rats to 12-18 mg in baboons, showing a difference among species.[3]

The aim of this study was to look at the amount of FK 506 used in human organ transplantation and the current maintenance doses of FK 506 and steroids in these patients.

MATERIALS AND METHODS

All of the patients at the University Hospital of Pittsburgh who received FK 506 as immunosuppression from February 28 to October 16, 1989, were included in the study. The details of FK 506 rescue and primary immunosuppression are given elsewhere in this symposium.

There were 17 patients enrolled in FK 506 trials from February to August 1989. An additional 46 patients were entered in September and another 48 patients were entered by October 16, 1989; a total of 111 patients were given FK 506 (Fig 1). This number includes 6 children (9 months to 13 years of age). One hundred two liver transplants, 9 kidney transplants, 5 pancreatic transplants, 3 heart transplants, and 2 double lung transplants are included. Ten patients received more than one allograft (4 kidney/liver, 4 pancreas/liver, 1 pancreas/liver/kidney, and 1 lung/liver).

All of the patients were monitored with measurements of trough plasma level of FK 506.[4,5] Of the 111 patients treated with FK 506, 11 patients were removed from therapy. Eight patients died and 3 patients had the FK 506 stopped because of allograft nephrectomy. Thus, a total of 100 patients were available to study the maintenance dose of FK 506 and steroids.

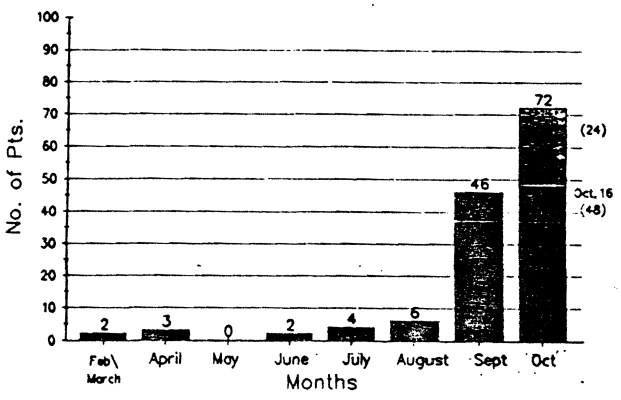

Fig 1. The number of organ transplant recipients per month started on FK 506.

Dosage

The initial dosage schedule is shown in Table 1. FK 506 was given as a single intravenous dose (0.15 mg/kg) over 1-2 hours on the first day. On the second and third days, intravenous FK 506 was given at 0.075 mg/kg at 12-hour intervals. The oral dose commenced on the fourth day (or later if the patient was not able to tolerate oral intake) at 0.15 mg/kg twice a day. In general, there was often an overlap period of intravenous and oral doses for 12-36 hours.

RESULTS

Changes in FK 506 Dosing

Adjustments of the oral FK 506 dose were made in each patient according to the response of graft function, patient tolerance of the drug, side effects of immunosuppression, and plasma trough levels of FK 506. During the adjustment period, the oral dose was doubled in 7 patients for 1-3 weeks. In the other 93 patients, the dose was either reduced or maintained.

In 3 patients, it was decided to commence with oral doses of FK 506 without intravenous FK 506 therapy. In 4 patients, including 2 children, intravenous therapy was discontinued after 2-3 doses.

The present maintenance doses of FK 506 are based on 0.15 mg/kg given at varying intervals. Thirty-five patients (35%) received the FK 506 dose twice a day, 49 patients (49%) received FK 506 once a day, 11 patients (11%) received FK 506 every other day, 4 patients (4%) received

Table 1. Initial Dosage of FK 506 In All Patients

Days	Route	Dosage (mg/kg)	Frequency (Per Day)
1	IV	0.15	1
2 and 3	IV	0.075	2
4 and 5	Oral	0.15	2

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Table 2. Present Maintenance Dose of FK 506 of 0.15 mg/kg

Patients (%)	Frequency in Hours
35 (35)	12
49 (49)	24
11 (11)	48
4 (4)	72
1 (1)	168

the dose every third day, and 1 patient (1%) remained on a FK 506 dose once a week (Table 2).

Concomitant Use of Other Immunosuppressive Agents

CyA was continued in the first 14 FK 506 rescue patients, often at reduced doses, up to 3 days in 5 patients and up to 10 days in an additional 5 patients; it was discontinued in all the patients by the 12th day, except in one patient in whom low-dose CyA was continued for 7 weeks. In subsequent FK 506 rescue patients, CyA was discontinued before commencing FK 506 because of increases in daily trough levels of whole blood CyA, resulting in elevations of serum creatinine.[6]

Azathioprine was discontinued in all patients receiving it prior to FK 506 conversion. In 2 patients given FK 506 as primary immunosuppression, azathioprine was added for refractory rejection. Steroid doses were continued for the first 5 days, then reduced depending on the response in the rescue group. In the primary transplant group, 1 g of methylprednisolone was given intravenously on revascularization of the graft: 200 mg on the first day, with a daily 40-mg reduction until the fifth day. A 20-mg/d dose was maintained. Subsequent doses of steroids were reduced in the primary group according to graft function and the overall clinical situation. Patients with lung allografts were not given steroids postoperatively.

The present maintenance dose of steroids is 20 mg prednisone/d in 6 patients, 15 mg/d in 3 patients, 10 mg/d in 39 patients, and 5 mg/d in 36 patients. Sixteen patients have been maintained without any steroids (Table 3).

FK Levels

The daily plasma trough levels of FK 506 were determined in the first 65 patients given maintenance oral doses of FK 506. A total of 382 observations in the 65 patients are summarized in Table 4. Sixty-five percent of these FK 506 trough levels were <1 ng/ml, while 83% of such determinations were <2 ng/ml.

Table 3. Present Maintenance Dose of Prednisone

Patients (%)	Dose (mg/d)
6 (6)	20
3 (3)	15
39 (39)	10
36 (36)	5
16 (16)	0

Table 4. Plasma FK 506 Trough Levels (ng/ml) With Oral Dose (N = 382)

Level	<1	1-2	2-4	4-6	>6
%	65	18	8	4	5

DISCUSSION

As with any new drug, dosage can be difficult to determine. This is especially true for immunosuppressive agents, because with over-dosage there is a risk of infection, drug toxicity, and even the development of neoplasms. With underdosage, rejection could occur.

A dose of 0.15 mg/kg/d was initially chosen to study the safety profile and to obtain pharmacokinetic profiles. This was found to be a therapeutic dose in humans. The requirement for maintaining FK 506 immunosuppression is flexible. Some patients appear to be adequately immunosuppressed with half of the initial oral FK 506 dose or less. Routine use of azathioprine is not necessary and use of CyA should be avoided.

The maintenance dose of steroids was low. Since the majority of FK 506 patients have been followed for a short period, it is probable that the requirement of steroids can be smaller still. At present, over 52% of patients are either receiving no steroids or only 5 mg of prednisone daily; only 9% of patients are taking more than 10 mg/d of prednisone.

In conclusion, relatively low maintenance doses of FK 506, along with low doses of steroids, are adequate to achieve immunosuppression in human organ transplantation. Concomitant use of azathioprine is not necessary in our experience, and simultaneous use of CyA should be avoided.

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