Transplant Int (1992) 5 [Suppl 1]: S 524–S 528

TRANSPLANT
International

Japanese study of kidney transplantation: 1. Results of early phase II study

Japanese FK 506 Study Group

Abstract. For a 4-month period from July to October 1990, 37 primary renal transplant patients were enrolled in the early phase II study of FK 506. An i.v. dose of FK 506 0.075 mg/kg twice a day was administered initially, and then in oral dose of 0.15 mg/kg twice a day followed. Prednisolone was started at 1 mg/kg daily as an additioned drug. Some 32 live related donors with one-mismatched haplotype of HLA and 5 cadaveric donors underwent transplantation. All patients are alive, and all kidney allografts are functioning. A correlation between the trough level of FK 506 in whole blood and acute rejection or adverse events was retrospectively investigated. There was a significant correlation between the trough level in whole blood and acute rejection or renal impairment. In conclusion, the therapeutic dose of FK 506 should be adjusted by monitoring the trough level in whole blood, the range of which might be recommended to be 15–20 ng/ml during the early phase after transplantation.

Key words: FK 506 – Renal transplantation – Monitoring

FK 506 was introduced in liver transplantation in 1989 [1, 2, 6]. Only one preliminary pilot study in Pittsburgh on the prophylactic effect of FK 506 on kidney transplantation was reported in 1990 and 1991 [5, 7]. The results of an early phase II study of FK 506 on kidney transplantation performed by the Japanese Multicenter Study Group has recently been reported [3, 4]. The present paper focuses on the detection of an optimal therapeutic window of the FK 506 blood concentration in kidney transplantation evaluated, retrospectively, by monitoring the FK 506 trough level in whole blood of 36 enrolled renal transplant patients.

Offprint requests to: M. Ishibashi, M.D., Department of Urology, Osaka University Medical School, Fukushima 1-1-50, Fukushima-ku, Osaka 553, Japan

Materials and methods

Inclusion criteria. Excluded from the study were the following renal transplant recipients: (1) patients aged under 16 years old, (2) patients who had liver dysfunction as indicated by more than 1.6 mg/dl total bilirubin or twice or more glutamine-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) values than normal, (3) patients who had cardiac problems, with less than 60% of ejection fraction or an abnormal EKG, (4) patients who had pulmonary dysfunction of less than 70 mm Hg of PaO_2, (5) patients who had a history of pancreatitis or diabetic nephropathy, (6) patients who had a peptic ulcer, (7) patients who had a history of or currently had a malignant diesease, (8) patients who had infectious disease such as hepatitis B (HB) virus hepatitis or a carrier status of HB human immunodeficiency virus (HIV), or syphilis, (9) patients who had drug hypersensitivity or allergy, (10) patients who were pregnant or were expected to become pregnant, (11) patients who had undergone a previous kidney transplantation, (12) patients who had a minor mismatch for ABO blood group, (13) patients who had a positive T-cell crossmatch, (14) patients who received related, HLA identical or HLA nonidentical in 2-haplotype, sibling donor, or nonrelated living donor, (15) patients who did not consent to receive the FK 506 treatment.

Patients background. In all, 37 renal transplant patients were enrolled in this study. The mean age of the donors and recipients was 55.3 ± 7.6 and 31.6 ± 8.4, respectively. Some 31 received renal allograft from related, living, one HLA-haplotype mismatched donors, and 6 received them from cadaveric donors. One patient was excluded because of an unsuitable entry criteria (mismatch for ABO blood group). The PRA grade was 0% in 31 patients, less than 10% in 4, and undetectable in 1. The mean number of mismatched antigens of HLA-A, -B, and -DR were 1.8 ± 1.0.

Dosage of FK 506 and concomitant steroid. An initial dose of FK 506 0.15 mg/kg daily was administered intravenously over 4 h in 2 divided doses after revascularization, followed a few days later by 0.30 mg/kg orally divided info 2 doses. The daily dose of FK 506 was adjusted depending on the patients' clinical status or the severity of the acute rejection, with an upper limit (not to be exceeded) of 0.25 mg/kg twice a day. Prednisolone was used in combination with FK 506. On day 0 a bolus dose of 250 mg of methylprednisolone was administered, followed by 50 mg/day of prednisolone between days 1 and 6, 30 mg/day between days 7 and 13, 20 mg/day between days 14 and 20, 15 mg/day between days 21 and 27, and 10 mg/day from day 28 on.

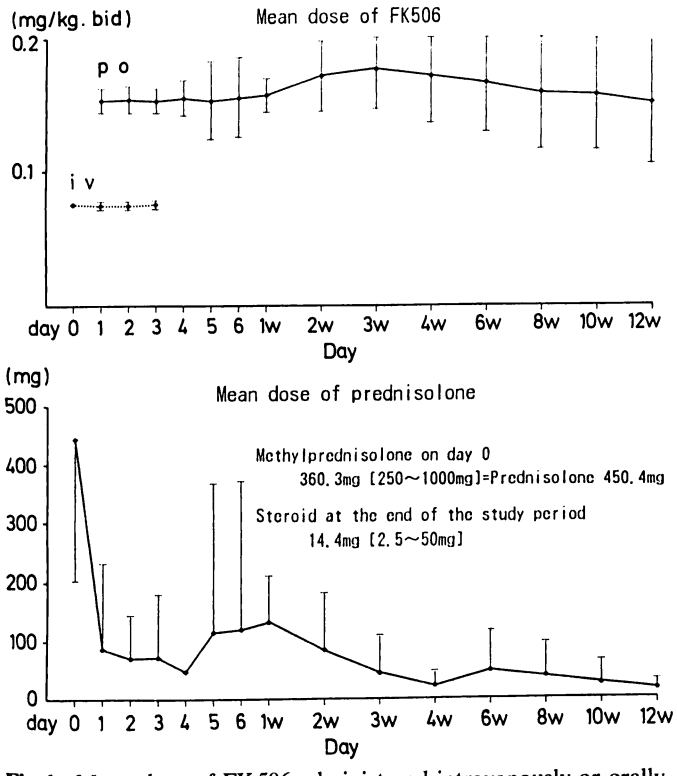

Fig. 1. Mean dose of FK506 administered intravenously or orally and that of prednisolone administered including a bolus dose of methylprednisolone for 12 weeks of posttransplantation therapy in 36 enrolled transplant recipients

Monitoring of blood concentration. Trough levels of FK506 in whole blood were monitored by the double sandwich enzyme-linked immunosorbent assay (ELISA). The procedure for the extraction of the blood sample was performed using dichloromethane.

Criteria of renal impairment. Renal impairment induced by FK506 was diagnosed by a pathology study of a specimen taken by graft biopsy. The diagnosis was made from foamy vacuolization of proximal tubular cells, especially in the straight portion, calcification forming crystalloid in distal and/or proximal tubules, and a scanty vacuolization of the arteriolar wall.

Results

Mean dosage of FK506 and prednisolone

The mean dosage of FK506 in the transplant recipients enrolled during the first 3 months was calculated by their body weight every week (Fig. 1). The mean dosage of intravenous FK506 during the first 3 days was 0.075 ± 0.002 mg/kg twice a day, and subsequently the oral dosage was about 0.16 ± 0.03 mg/kg twice a day up to 12 weeks. The increment of mean oral dosage of FK506 in weeks 2–3 was explained by the relatively decreasing body weight after transplantation. On day 0, the mean dose of prednisolone was 442.6 ± 238.9 mg/day, and the dosage was increased twice at 1 and 6 weeks after transplantation. Steroid therapy was not withdrawn in any patient during the 12 weeks post-transplantation. The mean steroid dose at the end of the study period was 14.4 mg/day.

Patients and graft survival

At the end of the study, all 35 patients evaluated for efficacy were alive. All kidney allografts of the 23 patients who were able to continue taking FK506 for 12 weeks and of the 12 patients who changed to another regimen owing to adverse effects or rejection were functioning 3 months after transplantation.

Monitoring of FK506 blood concentration as related to rejection or adverse effects

To find an optimal blood concentration of FK506 for kidney transplantation therapy, a correlation between its trough level in whole blood and episodes of rejection or adverse effects was investigated. Furthermore, to understand the drug monitoring of FK506 in renal transplantation, a pharmacokinetics study was performed in 12 patients.

1. Pharmacokinetics of FK506 in renal transplant patients: A pharmacokinetics study of the FK506 whole blood concentration after either intravenous (10 patients) or oral (12 patients) administration was studied and reported in a previous paper [4]. All patients had normal liver function in the study. In brief, the mean $AUC_{(0\text{–}12\,h)}$ (area under the blood concentration-time curve) of i.v. administration of 0.075 mg/kg for 4 h, was 481 ± 129 (300–758) ng · h/ml and that of oral administration of 0.15 mg/kg was 249 ± 180 (95.1–743) ng · h/ml, for whole blood level. As shown in Fig. 2, variations in the absorption and excretion of all the FK506 among the patients were noticed, while variations in the blood concentration on i.v. administration were minimal in patients with normal liver function except 1. Therefore, monitoring of the blood concentration of FK506 should be strongly recommended, when administered orally, if there is a significant correlation between the trough level of FK506 and clinical manifestations such as adverse events or onset of acute rejection.

2. Episodes of acute rejection and adverse events under the FK506-prednisolone regimen:
Of the 35 patients, 26 rejection episodes were observed in 16 patients (45.7%, 1.63 episodes per patient). The incidence of steroid-resistant rejection of 26 rejection episodes was 30.8% (9 episodes). As shown in Fig. 3, there were two peaks of rejection episodes. The first one occurred between days 7 and 13, involving 8 episodes (22.9%) in the 35 patients treated with FK506, but only 1 episode was steroid-resistant. The second peak occurred between days 28 and 55, and 9 episodes (28.1%) were noted in the 32 patients treated with FK506, of which 4 were steroid-resistant.

Of the 36 patients enrolled, renal impairment (44.8%), abdominal distension (30.6%), cardiac symptoms (27.8%) such as chest pain, chest discomfort, palpitation, abnormal EKG, decreased ejection fraction, and tachycardia, hyperkalemia (27.8%), tremor (27.8%), and hyperglycemia (25.0%) were found. The incidence of three major adverse events, renal impairment, cardiac

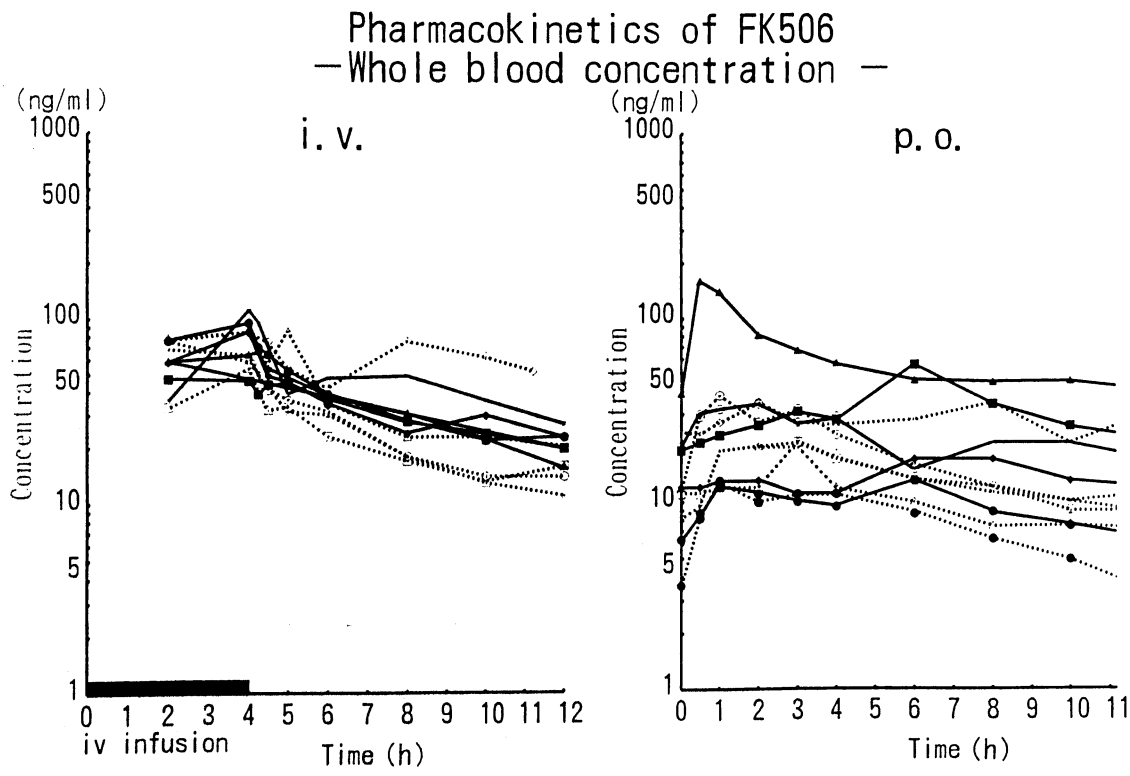

Fig. 2. Pharmacokinetics study of FK506 therapy in renal transplant recipients with normal liver function was done in 10 patients with a i.v. dose of 0.075 mg/kg of FK506 in a 4-h infusion and in 12 patients with a p.o. dose of 0.15 mg/kg FK506

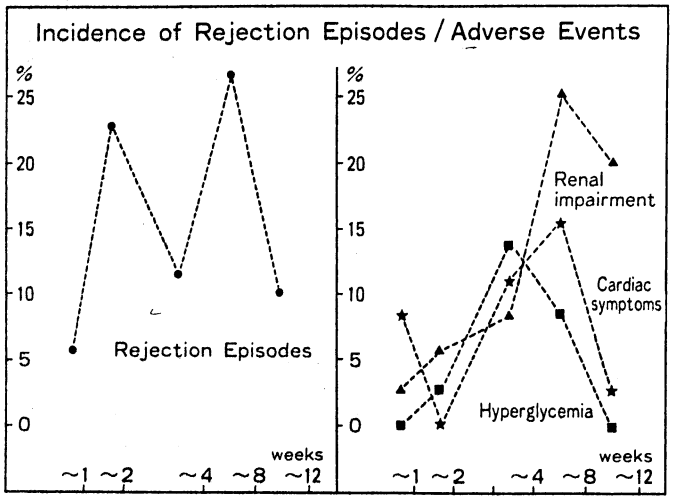

Fig. 3. Incidence of rejection episodes or adverse events in transplant patients under FK506 administration. Incidence of episodes was calculated as follows: ratio of episodes observed to numbers of patients administered FK506 at the time of diagnosis of the episodes

symptoms, and hyperglycemia, is shown in Fig. 3 and was seen to be high between weeks 3 and 10.

3. Correlation between FK506 whole blood trough level and rejection or three major adverse events:

Figure 4 depicts a correlation between the FK506 whole blood trough level and major clinical manifestations under FK506 immunosuppression. As to rejection episodes, the background of patients with or without rejection was investigated (Table 1). There was no correlation between donor ages, HLA antigens mismatched, or total amount of prednisolone administered within 7 days. However, the trough level in whole blood during weeks 1–2 posttransplantation in patients with acute rejection was significantly lower than that in patients without acute rejection. As shown in Fig. 4, a significant difference between the mean trough level in whole blood in patients without rejection and that in patients with rejection was noticed. Therefore, the data implied that most of the rejection episodes appearing within 1–2 weeks (Fig. 3) were considered to be due to a suboptimal range of FK506 blood concentration. The comparison between adverse events and FK506 trough level in whole blood was made. Patients who had adverse events such as renal impairment, hyperglycemia, and cardiac symptoms always showed a higher trough level in whole blood, over 20 g/ml.

Conversion of FK506-prednisolone to conventional immunosuppression

Twelve patients (32.4%) converted from the FK506-prednisolone regimen to another regimen. Nine of them discontinued using FK506 because of rejection or adverse events. Figure 5 shows the reasons for the regimen change and the time that the FK506 stopped or combined with another immunosuppressant. About 6–11 weeks post-transplantation, the FK506-prednisolone regimen was changed frequently. The reasons for the regimen change were mainly rejection and renal impairment. Of the 9 pa-

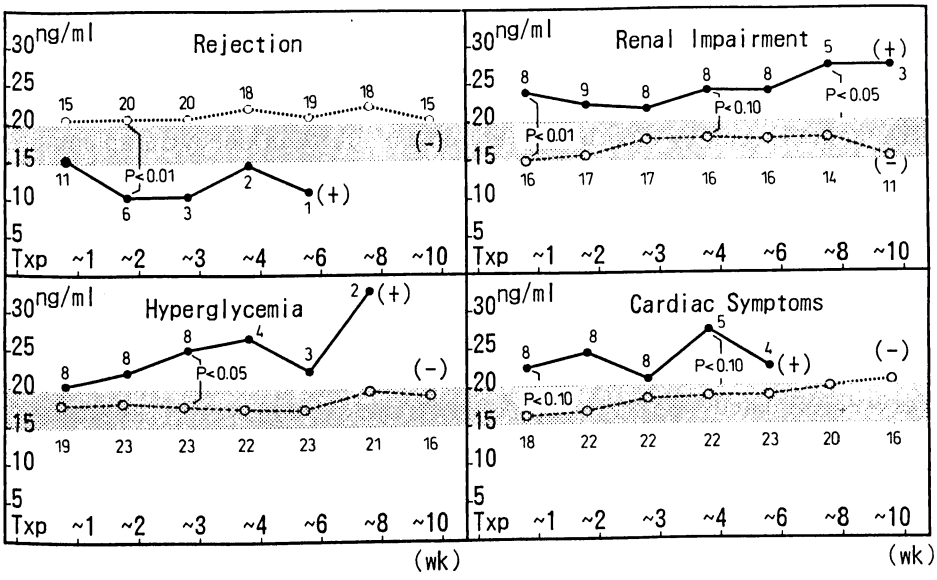

Fig. 4. A correlation between mean trough level of FK 506 in whole blood and clinical manifestations such as acute rejection, renal impairment, hyperglycemia, or cardiac symptoms. In the comparison of trough level at each episode observed, numbers of patients without episode (−) and with episode (+) are given. A statistical analysis between the two groups was performed by Student's *t*-test

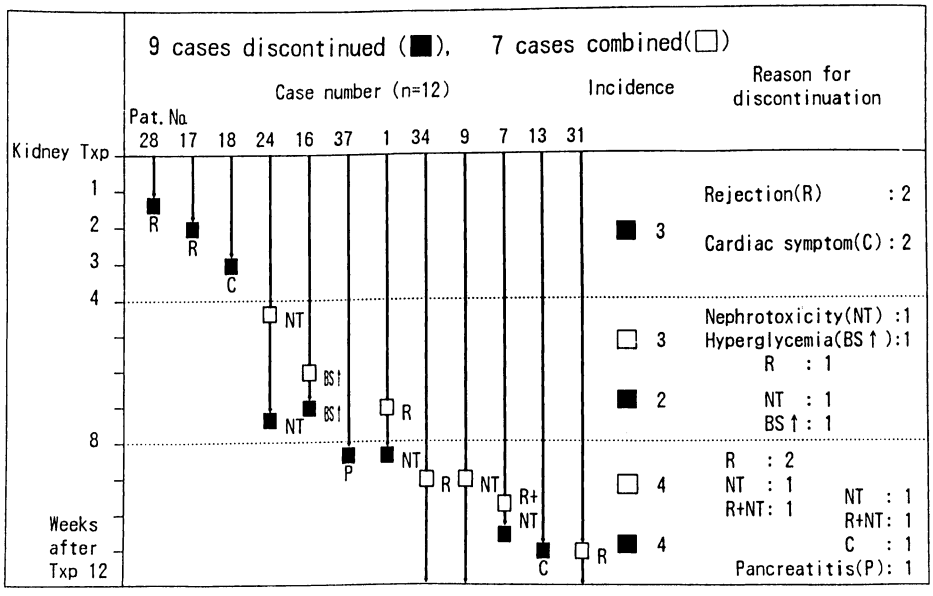

Fig. 5. Of the 36 cases evaluated, 12 (32.4%) changed the FK 506-prednisolone regimen during the first 12 weeks post-transplantation

Table 1. Background of patients undergoing FK 506-prednisolone therapy

	Acute rejection		Significance
	With (n = 16)	Without (n = 20)	
Donor age	57.5 ± 8.1	53.4 ± 6.9	NS
HLA antigens mismatched			
A + B	1.3 ± 0.7	1.3 ± 0.9	NS
DR	0.5 ± 0.5	0.5 ± 0.5	NS
A + B + DR	1.8 ± 0.9	1.8 ± 1.1	NS
PRA grade (%)	8.6 ± 9.7	2.9 ± 7.2	NS
Total dosage of steroid (mg) (days 0~7)	840.0 ± 296.9	828.7 ± 189.4	NS
Trough level in whole blood (ng/ml) (1–2 weeks post-Tx)	11.6 ± 4.6 (n = 8)	20.6 ± 12.4 (n = 20)	$P < 0.01$

tients who discontinued, 5 stopped taking FK 506 for rejection or renal impairment (2 patients for rejection, 1 patient for rejection plus renal impairment, and 2 patients for renal impairment), and the remaining 4 patients discontinued because of other adverse events (2 patients for cardiac symptoms, 1 patient for hyperglycemia, and 1 patient for pancreatitis). Of the 7 patients receiving FK 506 with other immunosuppressants, 3 who were given FK 506 up to week 12 gave rejection or renal impairment as the reason for the regimen change.

Discussion

The Japanese FK506 Study group has already reported the benefit of monitoring the FK506 trough level in whole blood after kidney transplantation [4]. The monitoring of the FK506 level in whole blood is superior to that in plasma and the reason is as follows:

1. Distribution of FK506 in plasma is temperature-dependent
2. Concentration of FK506 in plasma is markedly lower than in whole blood
3. Fluctuation of the FK506 concentration is more prominent in plasma than in whole blood
4. FK506 trough level in whole blood was well correlated with clinical manifestations including rejection episodes and adverse events.

The present early phase II study on kidney transplantation has confirmed the significantly important value of monitoring the FK506 trough level in whole blood. With respect to acute rejection, the trough level in whole blood during weeks 1–2 posttransplantation was noticed to be a significant factor in the background of patients with or without rejection during the first 12 weeks posttransplantation. Although FK506 has adverse effects such as renal impairment, hyperglycemia, or cardiac symptoms, its trough level in whole blood was significantly correlated with these adverse events. In addition to the obvious correlation between the trough level in whole blood and clinical manifestations such as rejection and adverse events, the pharmacokinetics study in kidney transplant patients without liver dysfunction has produced the useful information that there were variations in the trough level during FK506 oral administration between individual transplant renal recipients, which indicates the importance of FK506 monitoring.

The early phase II study was tentatively implied an optimal therapeutic dose of FK506 in kidney transplantation therapy, and the range between 20 and 15 ng/ml for the trough level in whole blood during the first 3 months is recommended.

References

1. Fung JJ, Todo S, Jain A, McCauley J, Alessiani M, Scotti C, Starzl TE (1990) Conversion of liver allograft recipients with cyclosporine related complications from cyclosporine to FK506. Transplant Proc 22: 6–12
2. Jain AB, Fung JJ, Todo S, Alessiani M, Takaya S, Abu-Elmagt K, Tzakis A, Starzl TE (1991) Incidence and treatment of rejection episodes in primary orthotopic liver transplantation under FK506. Transplant Proc 23: 928–930
3. Japanese FK506 Study Group (1991) Clinicopathological evaluation of kidney transplants in patients given a fixed dose of FK506. Transplant Proc (in press)
4. Japanese FK506 Study Group (1991) Japanese study of FK506 on kidney transplantation: the benefit of minitoring the whole blood FK506 concentration. Transplant Proc (in press)
5. Shapiro R, Jordan M, Fung J, McCauley J, Johnston J, Iwaki Y, Tzakis A, Hakara T, Todo S (1991) Kidney transplantation under FK506 immunosuppression. Transplant Proc 23: 920–923
6. Starzl TE, Todo S, Fung J, Demetris AJ, Venkataramanan R, Jain A (1989) FK-506 for human liver, kidney and pancreas transplantation. Lancet II: 1000–1004
7. Starzl TE, Fung JJ, Jordan M, Shapiro R, Tzakis A, McCauley J, Johnston J, Iwaki Y, Jain A, Alessiani M, Todo S (1990) Kidney transplantation under FK506. JAMA 264: 63–67