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ORIGINAL ARTICLE

Shiro Takahara
Tsuneharu Miki
Motoaki Hatori
Yukito Kokado
Jingding Wang
Akihiko Okuyama

A comparative study of FK506 granules and capsules in renal transplant recipients

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S. Takahara (✉) · T. Miki
M. Hatori · Y. Kokado
J. Wang · A. Okuyama
Department of Urology,
Osaka University Medical School,
Yamada-oka 2–2, Suita-City,
Osaka 565, Japan
Fax: + 81-6-869-3539

Abstract Nine renal transplant recipients in stable systemic condition on FK506 capsules were converted to FK506 granules in order to investigate the safety, efficacy, and pharmacokinetics of the granular formulation of FK506. The study period for the administration of FK506 granules was 4 weeks, and in principle, the oral dose was the same as that of the FK506 capsules. Renal graft function remained stable and no rejection signs were noticed while the patients were taking the granules. The area under the blood concentration-time curve (AUC), the maximum blood level (C_{max}), and the time to reach C_{max} (T_{max}) after FK506 capsules and FK506 granules were, respectively, 93.1 ± 66.4 and 97.0 ± 89.1 ng · h/ml (P = 0.81), 12.7 ± 7.1 and 15.2 ± 11.7 ng/ml (P = 0.39), and 2.0 ± 1.7 and 1.3 ± 0.6 h (P = 0.29). The mean trough blood level during FK506 medication was 4.25 ± 3.42 and 4.02 ± 3.83 ng/ml, respectively, for the capsules and the granules. FK506 granules, a new formulation, showed an efficacy comparable to that of the FK506 capsular formulation.

Key words FK506 granules · FK506 capsules · Pharmacokinetics, FK506 granules

Introduction

FK506 (tacrolimus) is a novel macrolide lactone with potent immunosuppressive properties [6, 7]. It has been proved effective in suppressing graft rejection in kidney [10], liver [2, 11], and bone marrow [9] transplantation, and studies suggest that it is also effective in heart, lung, and intestinal transplantation [1, 3, 12]. At present, FK506 capsules are usually administered. For reasons of safety and efficacy, FK506 trough levels are gradually decreased over time, and the average maintenance dose of FK506 for renal transplant recipients after 2 years posttransplantation has been reduced to less than half of the initial dose [5]. It is necessary to reduce the dose even further in renal transplant recipients with stable functioning grafts, possibly by developing a new formulation of FK506 that would allow for fine dosage adjustment. In Japan, the majority of patients who undergo liver transplantation are children who receive livers from living donors. Many bone marrow transplant recipients are also children. As capsules are not an adequate oral formulation for children, a new, easy-to-swallow formulation is needed.

To meet these clinical needs, FK506 granules have been developed. The present study was undertaken to investigate the safety, efficacy, and pharmacokinetics of FK506 granules in renal transplant recipients in stable systemic condition who are already under treatment with FK506 capsules.

Materials and methods

Nine patients who had undergone renal transplantation in our hospital were enrolled in this open, clinical trial that was conducted between May and October 1995. The subjects were selected from patients aged 16 years and older who had undergone transplantation at least 6 months prior to enrollment in the study and whose general condition and graft function were stable.

Table 1 Patient characteristics

Patient no.	Sex	Age (years)	Renal graft	Dose (mg/dose)	Duration of FK506 medication before conversion (months)
1	Male	43	Living donor	2	49
2	Male	44	Living donor	1	27
3	Male	33	Living donor	3	60
4	Male	25	Living donor	1	44
5	Female	43	Living donor	1	34
6	Male	51	Living donor	2	49
7	Female	43	Cadaveric donor	1[a]	33
8	Male	26	Living donor	1	29
9[b]	Male	36	Living donor	3	30
Mean ± SD	–	38.2 ± 8.8	–	1.7 ± 0.9	39.3 ± 11.5

[a] This patient received medication once a day, whereas the others received it twice daily
[b] This patient was converted to FK506 medication after an adverse event during CyA medication

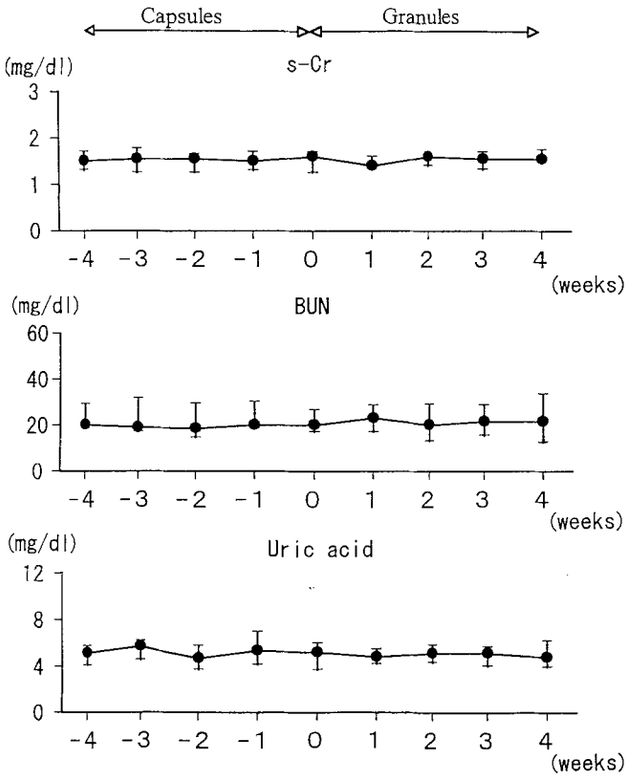

Fig. 1 Changes in parameters of renal function after oral dosing of FK506 capsules and FK506 granules in renal transplant recipients. Closed circles and bars represent median and Q1–Q3, respectively (*s-Cr* serum creatinine, *BUN* blood urea nitrogen)

The mean age ± SD of the patients (7 men, 2 women) was 38.2 ± 8.8 years; all but one patient had received a kidney from a living donor. By the time of their enrollment, the patients had already been taking FK506 capsules for a mean period of 39.3 ± 11.5 months (range 26–60 months). Eight patients had been treated with FK506 capsules since the operation while one patient had been switched to FK506 capsules after an adverse event during treatment with cyclosporin (CyA).

Prior to conversion to FK506 granules, which were administered for 4 weeks, the patients had received the same dose of FK506 capsules for at least 4 weeks. Five patients were administered 1 mg FK506, four of them twice daily and one once daily; two patients each were administered 2 mg and 3 mg, twice daily (Table 1).

The incidence and severity of symptoms of rejection and graft function [serum creatinine (s-Cr), blood urea nitrogen (BUN), and uric acid] during treatment with the granules were compared with those observed during the 4 weeks prior to conversion. In general, hematological tests, blood biochemistry tests, urinalysis, and FK506 blood level and trough concentration at 12 h after dosing were measured once or twice each week. The pharmacokinetic parameters were determined on the day prior to conversion to the granular formulation and on the 7th day after conversion, right before the morning dose and at 0.5, 1, 2, 3, 4, 8, and 12 h after it. The blood concentration of FK506 was measured by ELISA, as described by Kobayashi et al [8].

The FK506 blood concentration-time data were used to determine the maximum blood concentration (C_{max}) and the time to reach the maximum concentration (T_{max}). The area under the blood concentration-time curve (AUC) was calculated by the trapezoidal method. Differences between the two groups were statistically analyzed using Student's paired *t*-test.

Results

During treatment with FK506 granules, neither rejection episodes nor graft dysfunction was observed in any of the patients. No significant changes in parameters of renal function (s-Cr, BUN, uric acid) were observed during treatment with the granular formulation as compared with the values obtained before conversion (Fig. 1). Adverse reactions or abnormal deviations in clinical laboratory tests were not observed after the conversion.

Pharmacokinetic parameters after treatment with each formulation are summarized in Table 2, and individual FK506 blood concentration-time curves before and after conversion are shown in Fig. 2. Except for

Table 2 Pharmacokinetic parameters after oral administration of FK506 (capsules, granules)

Patient no.	Formulation	Dose		T_{max} (h)	C_{max} (ng/ml)	AUC_{0-12h} (ng · h/ml)	C_{12h} (ng/ml)	Ratio (granules/capsules)	
		mg	mg/kg					C_{max}	AUC_{0-12h}
1	Capsules	2	0.03	1	10	42.7	2.2	1.80	2.21
	Granules			2	18	94.4	4.5		
2	Capsules	1	0.02	2	10	70.2	3.1	0.93	0.98
	Granules			2	9.3	68.6	3.6		
3	Capsules	3	0.06	2	27	165.4	7.8	0.85	0.69
	Granules			1	23	113.3	5.2		
4	Capsules	1	0.02	0.75	14	105.6	6.9	0.51	0.40
	Granules			1	7.2	41.8	2.5		
5	Capsules	1	0.02	1	9.9	61.5	3.2	1.41	1.13
	Granules			1	14	69.2	2.3		
6	Capsules	2	0.03	0.5	13	92.0	4.2	1.00	1.13
	Granules			1.5	13	103.8	6.1		
7	Capsules	1	0.02	2	6.2	36.7	1.8	1.10	0.75
	Granules			0.5	6.8	27.6	0.94		
8	Capsules	1	0.02	3	4.1	32.6	1.5	0.93	1.05
	Granules			2	3.8	34.1	2.0		
9	Capsules	3	0.04	6	20	230.8	19	2.10	1.39
	Granules			1	42	320.0	14		
Mean ± SD	Capsules	1.7 ± 0.9	0.03 ± 0.01	2.0 ± 1.7	12.7 ± 7.1	93.1 ± 66.4	5.5 ± 5.5	1.18 ± 0.50	1.08 ± 0.51
	Granules			1.3 ± 0.6	15.2 ± 11.7	97.0 ± 89.1	4.6 ± 3.9		

Table 3 Mean trough blood concentration after oral administration of FK506 capsules or granules

Patient no.	Dose		Mean trough concentration (ng/ml)		Ratio (granules/capsules)
	mg	mg/kg	Capsules	Granules	
1	2	0.03	2.37 ± 0.31	3.15 ± 1.18	1.33
2	1	0.02	3.03 ± 1.44	2.60 ± 1.15	0.86
3	3	0.06	6.83 ± 2.64	4.18 ± 1.26	0.61
4	1	0.02	4.30 ± 2.46	3.15 ± 1.16	0.73
5	1	0.02	1.63 ± 0.55	2.00 ± 0.87	1.22
6	2	0.03	5.40 ± 3.39	5.90 ± 1.27	1.09
7	1	0.02	0.75 ± 0.67	0.53 ± 0.36	0.70
8	1	0.02	2.16 ± 0.34	1.35 ± 0.21	0.63
9	3	0.04	11.80 ± 2.08	13.33 ± 1.15	1.13
Mean ± SD	1.7 ± 0.9	0.03 ± 0.01	4.25 ± 3.42	4.02 ± 3.83	0.92 ± 0.28

one patient (no. 9) who showed faster absorption and elimination rates during treatment with the granular formulation, all of the patients showed comparable blood level profiles pre- and postconversion with minor differences.

No significant changes in the mean value of C_{max}, T_{max}, or AUC_{0-12h} were observed in any of the patients after conversion. After correction for dose level, the mean ± SD of the calculated C_{max} for 1 mg equivalent dose was 7.9 ± 3.1 ng/ml in the case of the capsular formulation and 8.7 ± 3.4 ng/ml in that of the granular formulation ($P = 0.58$); the AUC_{0-12h} for 1 mg equivalent dose was 56.2 ± 25.9 and 53.9 ± 24.4 ng · h/ml ($P = 0.80$), respectively.

The pharmacokinetics of each individual patient was further investigated by comparing the blood level profiles. The mean ± SD ratio of C_{max} and AUC_{0-12h} between the capsular formulation and the granular formulation was 1.18 ± 0.50 and 1.08 ± 0.51, respectively.

The trough blood concentration was 4.25 ± 3.42 and 4.02 ± 3.83 ng/ml, respectively, for capsules and granules, and the mean ratio of the blood level between the capsules and granules was 0.92 ± 0.28 (Table 3).

Discussion

FK506 is a new immunosuppressant that acts specifically on T cells to inhibit the production of cytokines such as IL-2 and subsequently the activation and proliferation of T cells [2, 3]. Clinical studies on FK506 in organ transplantation were initiated in 1989 in the United States, and nowadays FK506 is being marketed all over the world to suppress the rejection of liver and kidney grafts and for the treatment of graft-versus-host disease (GVHD) in bone marrow transplantation. Currently, FK506 capsules are the only formulation of the drug available for oral use, and the smallest dosage unit is

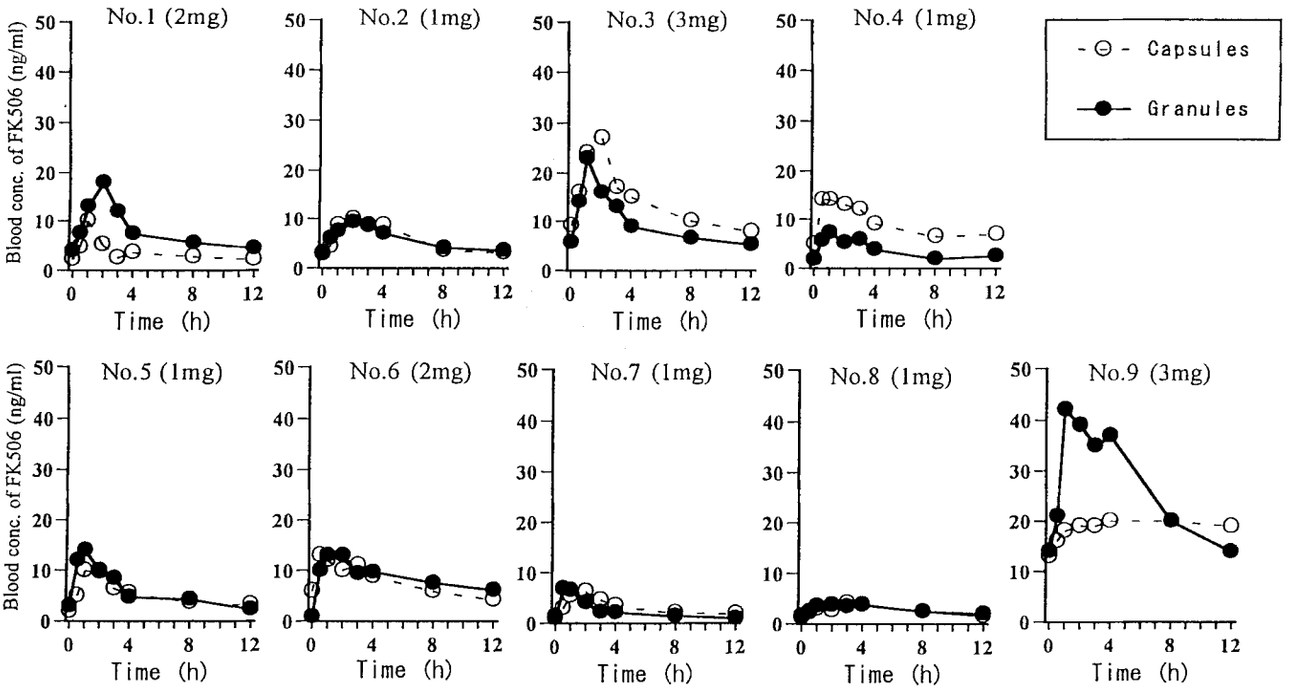

Fig. 2 Blood concentration of FK506 after oral dosing of capsules and granules in the nine renal transplant recipients

0.5 mg. As many patients undergoing liver or bone marrow transplantation are children, a new oral formulation suitable for children is urgently needed. At the same time, the survival of transplant recipients has increased in recent years and, consequently, patients are under immunosuppressive therapy for longer periods of time. Therefore, the current trend is to reduce the maintenance dose in order to avoid adverse reactions and ensure the safety of treatment. In this sense, even the smallest unit dose of the current capsules might not be adequate for a stepwise, fine adjustment of the maintenance dose. For these patients, a new formulation is also needed that would allow for fine dosage adjustment.

It was in response to these needs that FK506 granules were developed. Except for the addition of lactose in the granules, FK506 capsules and granules are practically equivalent formulations.

In this clinical trial, we investigated the safety, efficacy, and pharmacokinetics of FK506 granules. The nine patients enrolled in this study had undergone renal transplantation more than 2 years previously and had been under treatment with FK506 capsules at 0.02 ~ 0.06 mg/kg body weight, a much lower dose than the dose they were administered right after transplantation. For safety reasons, the maintenance dose for these patients may need to be reduced even further in the future. During the 4 weeks of FK506 granule administration, the grafts continued to function as they had before conversion, and adverse events were not observed.

Only one patient (no. 9) who had been converted to FK506 capsules from CyA medication showed some differences in blood concentration profile after conversion to the granular formulation. Since the patient took both capsules and granules before meals, the effect of food was excluded. Although an interindividual difference, which might have been due to the intraindividual difference [4], was observed, the ratio of C_{max} and AUC_{0-12h} between the granules and the capsules was 1.18 and 1.08, respectively. With regard to these ratios, the number of patients with a ratio above 1 and the number of patients with a ratio below 1 was about the same. Moreover, no significant difference in mean trough blood concentration was observed between the two formulations in any of the patients. These results suggest that there is no marked difference in the pharmacokinetics of the two formulations.

No signs of any problems regarding the safety or efficacy of the granular formulation were observed during this short clinical trial. Moreover, the fact that no significant differences were observed between the pharmacokinetic parameters of the two formulations suggests that the two formulations are virtually equivalent. We expect the FK506 granular formulation to become a medication of choice in the treatment of transplant patients. It will allow physicians to adjust the therapeutic doses of FK506 according to the conditions of each patient and will facilitate the compliance of pediatric patients.

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