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Early Trials With FK 506 as Primary Treatment in Liver Transplantation

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FK 506 was first used clinically in February 1989. It was given in an effort to salvage chronically rejecting liver grafts in patients who also had such poor renal function that optimal doses of CyA could not be given.[1]

THE FIRST LIVER TRANSPLANT UNDER FK 506

The second patient given the so-called rescue therapy had his liver graft salvaged, but eventually required emergency retransplantation because of thrombosis of a previously stenosed hepatic artery. This final graft was his sixth liver over a time span of 5 ⅔ years. The sixth transplantation, on July 2, 1989, was of historic interest because the new liver was the first one ever placed under immunosuppression solely with FK 506 to which low doses of steroids were added. This man is now 4 months postoperative after his last operation. He tolerated his sixth liver replacement with seeming ease despite poor renal function. His creatinine was 2.5 mg/dl at the time of his sixth liver retransplantation and is 2.3 mg/dl now. He has long since been home.

OTHER COMPLEX CASES

Another patient whose first graft could not be rescued with FK 506 also was successfully retransplanted almost 2 months ago, and a third patient became the recipient of a liver, pancreas, and kidney on August 16, 1989. All three of these patients are well, but the complexity of their indications for operation and the nature of their procedures made it difficult to compare their courses with anything in our recent experience. Consequently, we report the results of 20 consecutive primary liver transplantations performed between August 18, 1989, and the end of September 1989.

PRIMARY LIVER TRANSPLANTATION

Case Material

The individual cases are shown in Table 1. None of these operations involved either retransplantation or the transplantation of other organs. We picked from our past experience 20 other patients treated with conventional agents, including CyA, and made certain comparisons. For inclusion as a control, it was required that there be survival for at least 1 full month. This meant that the control cases were culled, whereas the test cases were not. The controls were matched for age, sex, original disease, and degree of urgency as defined by the UNOS scoring system.[2]

Immunosuppression

The management of the FK 506 patients was as described elsewhere in this symposium. A dose of 0.15 mg/kg FK 506 was given intravenously over 1 hour after the new liver was revascularized. The intravenous dose thereafter was 0.075 mg/kg/12 hours until the patient could eat. When a switch was made to the oral route, 0.15 mg/kg every 12 hours, the intravenous and oral doses overlapped for a day or two. Trough levels after a few days tended to be about 1 ng/ml or lower (Fig 1). One gram of methylprednisolone was given intravenously in the operating room and a rapid

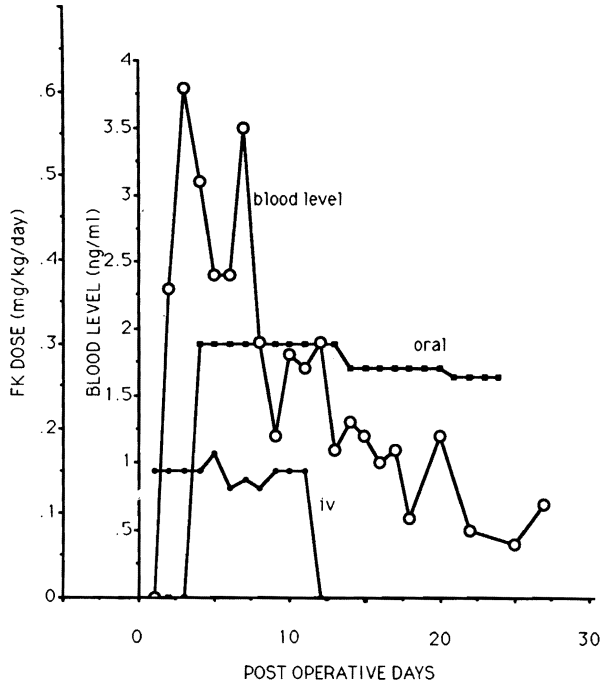

Fig 1. Daily dose and blood levels of FK 506 in patients after liver transplantation. I.V., intravenous dose; Oral, oral dose.

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Table 1. Summary of the First 20 Primary Liver Recipients Treated by FK 506

Patient No.	OLTX	Age	Sex	Indication	Latest Liver Function SGOT (U/L)	SGPT (U/L)	T. BIL (mg/dl)	Latest Immunosuppression FK 506 (mg/kg/d)	Steroid (mg/d)	Histologic Rejection	Follow-up Days	Comment
1	2108	55	F	PBC	55	31	1.4	0.18 × 2	20	0	14	Died of MI
2	2116	41	F	PNC-B	37	45	0.5	0.18 × 2	0	0	60	Discharged at 19 d
3	2121	38	M	PNC-C	56	72	0.2	0.15 × 2	5	0	50	Discharged at 12 d
4	2128	39	M	PNC-E	35	28	0.4	0.15 × 1	5	1	42	Discharged at 25 d
5	2130	49	M	SC	22	42	0.8	0.15 × 1	0	0	41	Discharged at 13 d
6	2127	43	M	PNC-C	82	129	0.6	0.15 × 1	0	0	41	Discharged at 17 d
7	2133	42	M	BC	17	8	0.7	0.16 × 2	0	0	40	Discharged at 10 d
8	2134	18	M	Alagille's disease	20	18	0.4	0.18 × 1	5	0	41	Discharged at 18 d
9	2138	41	F	PBC	72	80	0.9	0.11 × 1	5	1	38	Discharged at 15 d
10	2140	19	M	SC	255	545	9.5	0.25 × 2	20	3	34	Hospitalized for rejection
11	2143	33	F	PBC	299	382	0.9	0.18 × 1	5	1	32	Readmitted for rejection
12	2144	36	F	PNC-C	27	49	0.3	0.15 × 1	5	0	31	Discharged at 11 d
13	2145	38	M	PNC-C	28	72	1.2	0.18 × 1	5	0	31	Discharged at 14 d
14	2149	28	M	Caroli's disease	25	34	0.9	0.15 × 2	10	1	28	Discharged at 14 d
15	2150	41	M	PNC-E	33	25	0.5	0.17 × ½ d	5	0	27	Hospitalized
16	2151	31	M	SC	39	62	0.8	0.15 × 1	0	1	27	Discharged at 10 d
17	2152	64	F	PNC-E	54	194	0.6	0.15 × 1	10	0	25	Discharged at 8 d
18	2153	55	M	PNC-E	18	20	1.1	0.14 × 1	10	0	23	Hospitalized
19	2154	43	F	PNC-C	28	52	0.7	0.18 × 1	0	0	23	Discharged at 18 d
20	2156	49	F	BC	40	90	1.6	0.14 × 1	10	0	21	Discharged at 19 d

OTLX, orthotopic liver transplantation; T. BIL, total bilirubin; PNC, primary biliary cirrhosis; PNC-B, postnecrotic liver cirrhosis by B hepatitis; PNC-C, cryptogenic liver cirrhosis; PNC-E, alcoholic liver cirrhosis; SC, sclerosing cholangitis; BC, Budd-Chiari disease.

steroid taper from 200 to 20 mg/d was carried out over 5 days by 40-mg daily decrements. The FK 506-treated patients had a greatly reduced incidence of histopathologic rejection and almost no need for bolus or steroid recycle therapy or for other agents (Table 2).

The steroid doses in the FK 506 patients versus the CyA controls are summarized in Fig 2. The average dose in the 19 FK 506 recipients who lived throughout the month was 9 mg/d at the end of this time. In the controls, the dose averaged 19 mg/d. The summary data on all 20 patients are given in Table 1.

Mortality

One of the 20 test patients died. This recipient, who had an old myocardial infarction, had primary pulmonary hypertension with pulmonary artery pressures almost equal to the systemic blood pressure. The pulmonary hypertension was treated with prostaglandin infusions during the liver replacement and for 2 days afterward. Her recovery thereafter was unremarkable but, on the eve of her planned discharge, she developed signs of peritonitis. Her abdomen was explored, but there were no abnormalities. As the wound was closed, she had a cardiac arrest and could not be resuscitated. At autopsy, there was evidence of the old myocardial infarction, and she was found to also have a 90% stenosis of the left anterior descending coronary artery. The other patients are alive and well.

Liver Function

Liver functions were followed daily for the first 2 weeks and irregularly thereafter.

Bilirubin. The fall in bilirubin to normal was very rapid in the FK 506-treated patients, and this advantage was maintained throughout the study period. It averaged 1.0 mg/dl at 1 month versus 5 mg/dl in the controls (Fig 3).

SGOT. The SGOT after liver transplantation was similar in both groups of patients (Fig 4).

Gamma-Guanosine Triphosphate. This canulicular enzyme measurement started higher during the first few days in the FK 506-treated patients, but it fell rapidly and, at all

Table 2. Rejection and Immunosuppression

Group	N	Clinical and Histologic Rejection (%)	Steroids (Bolus/Recycle) (%)	Imuran (%)	OKT3 (%)
FK 506	20*	3 (15)	2 (10)	1 (5)	0 (0)
CyA	20	12 (60)	17 (85)	18 (90)	11 (55)

*One patient died of MI and severe pulmonary hypertension at postoperative day 14 with well-functioning liver graft.

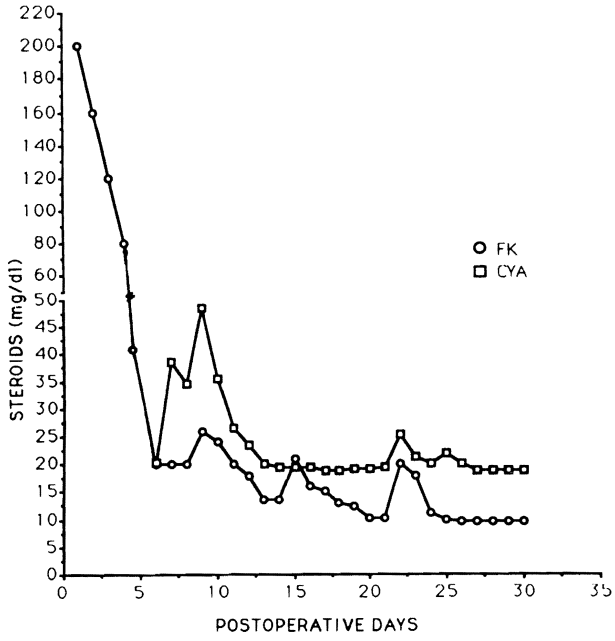

Fig 2. Differences of daily steroid dose given to FK 506 patients versus CyA patients.

times after 2 weeks, the values were lower than in the conventional controls (Fig 5). The same pattern of a late advantage (after 2 weeks) as noted with the gamma-guanosine triphosphate was also seen with the alkaline phosphatase (Fig 6).

DISCUSSION

The 20 patients who were the main object of our statistical studies were the first to be treated with FK 506 from the

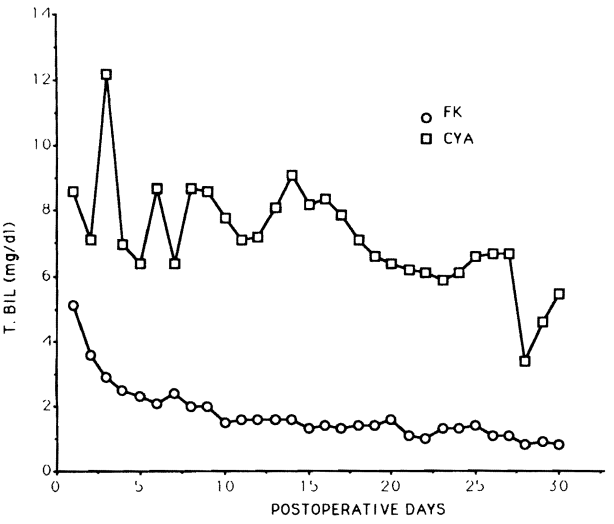

Fig 3. Postoperative changes of total bilirubin in FK 506 patients versus CyA patients.

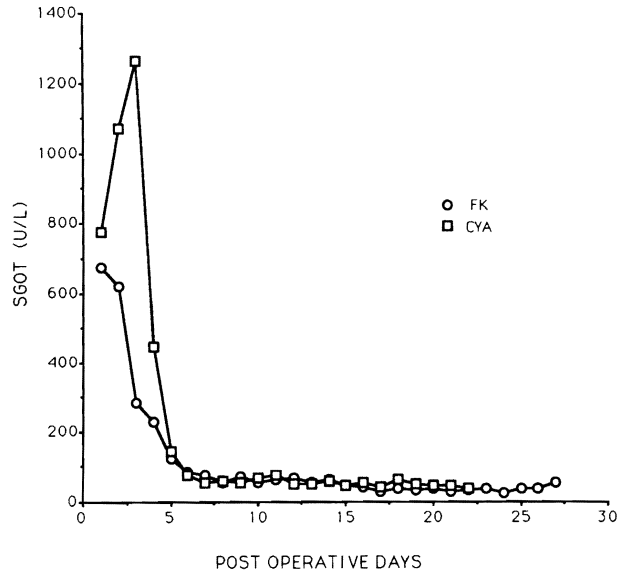

Fig 4. Postoperative changes of the SGOT in FK 506 patients versus CyA patients.

day of their operation. By the time of transplantation, there was no difficulty in recruiting participants in the study, since these new candidates had been exposed on an open ward to many of the patients whose livers had been rescued with FK 506. The very rapid convalescence of this new crop of fresh FK 506-treated patients, their low incidence of rejection, their low steroid requirements, and their early discharge from the hospital also became common knowledge. The rapidity and quality of convalescence of these first patients made it difficult to convince subse-

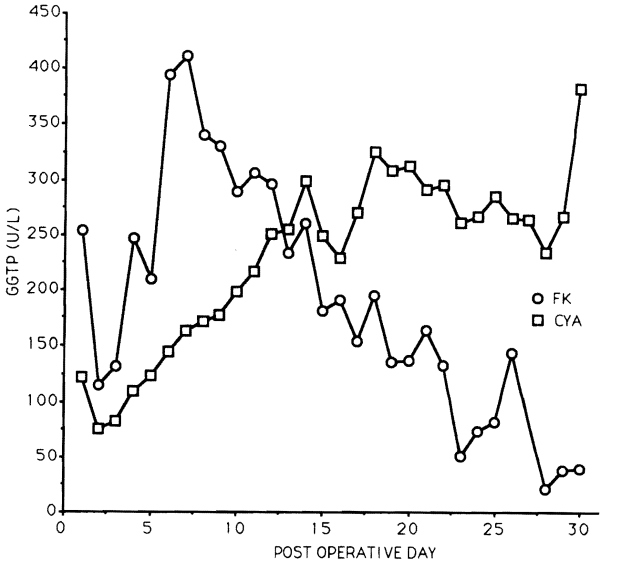

Fig 5. Postoperative changes of the GGTP in FK 506 patients versus CyA patients.

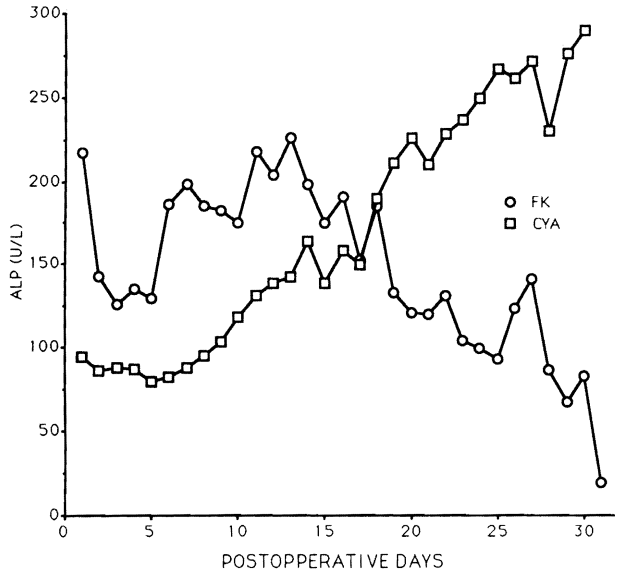

Fig 6. Postoperative changes of ALP in the FK 506 patients versus CyA patients.

quent patients to submit to so-called conventional immunosuppressive regimens. The consequence was case accrual to the FK 506 series in avalanche proportions.

Almost all aspects of these cases will be considered in other papers from this symposium. However, we would like to comment on one other detail, namely, the elimination of early graft failure (called by some "primary nonfunction") in patients treated with FK 506. We have defined primary nonfunction rather loosely as the need for retransplantation in the first 15 days. The incidence of this kind of retransplantation in the best centers has been 15 to 20%.[3,4] Of the first 46 livers transplanted under FK 506 up to 2 weeks ago, including 3 retransplants, 38 primary livers used alone, and 5 livers used as parts of clusters or in other organ combinations, not a single one has had primary nonfunction. This means that many, if not most, of the mysterious perioperative graft failures collectively called primary nonfunction probably have a major immunologic etiology rather than reflecting a preservation injury or technical misadventure.

REFERENCES

1. Starzl TE, Todo S, Fung J, et al: Lancet 1:1000, 1989

2. Starzl TE, Gordon RD, Tzakis A, et al: Transplant Proc 20:131, 1988

3. Starzl TE, Demetris AJ, Van Thiel DH: N Engl J Med 321:1014, 1989

4. Starzl TE, Demetris AJ, Van Thiel DH: N Engl J Med 321:1092, 1989