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One Hundred Ten Consecutive Primary Orthotopic Liver Transplants Under FK 506 in Adults

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FK 506 was introduced clinically as salvage therapy for patients with failing liver grafts.[1,2] Then in August 1989, a trial was started in which FK 506 was used as the primary immunosuppressant in fresh cases, combined with steroids, from the time of hepatic transplantation.[3,4] From then until mid-February 1990, 125 consecutive recipients entered the trial, of whom 110 were adults and 15 were children. This phase of the drug's development came to an end with the institution of a randomized trial in mid-February 1990. The results as of 1 April 1990 in all but 5 of these cases were previously reported.[4] Further follow-up of the pediatric case collection is being provided at this meeting by Tzakis et al.[5] We will account here for all of the original 110 adult liver recipients. Because follow-ups are to 15 August 1990, the observation period in surviving patients ranges from 6 months to 1 year.

METHODS

Case Material

The features of the 110 adult recipients are summarized in Table 1. These were similar to those in 325 consecutive adults treated with conventional immunosuppression from October 1987 to November 1988, except that there appeared to have been a higher representation recently of sicker candidates as reflected by the UNOS urgency classification.

The treatment protocol of FK 506 has been described in more detail previously.[4] Intravenous therapy was started at 0.15 mg/kg/d (in divided doses), and oral dosing was begun at 0.3 mg/kg/d, also in divided doses, as soon as alimentation was possible. These doses are still undergoing revision and cannot be considered final, as has been discussed elsewhere at this conference.[6] In the first half of the series, a 1 g bolus of prednisone was given intraoperatively, as well as a 5-day burst of prednisone beginning with 200 mg on the first postoperative day and ending with 20 mg/d on the 6th day. In the last part of the series, daily maintenance with 20 mg/d prednisone was used from the outset. Patients with rejection were treated as needed with augmentation of the FK 506 doses and/or maintenance steroid doses, 1 g of hydrocortisone or methylprednisolone, a 3- to 5-day course of 5 mg/d of OKT3, or in a few cases by the addition of azathioprine. Management was facilitated by protocol biopsies after approximately 2 postoperative weeks, and again at 2 months. Additional biopsies were taken for specific indications.

Table 1. Cases Receiving Consecutive Orthotopic Liver Transplantation Under the Treatment with FK 506* or Cyclosporine

	FK 506	CyA
N	110	325
Age	46 (18–70)	46 (18–73)
Male/female	58/52	178/147
Indication (%)		
Parenchymal	72 (65)	192 (58)
Cholestatic	28 (25)	81 (25)
Metabolic	5 (5)	8 (3)
Malignant	3 (3)	25 (8)
Others	2 (2)	19 (6)
UNOS score (%)		
1	0	19 (6)
2	25 (23)	61 (19)
3	43 (39)	160 (49)
4	15 (14)	48 (15)
4US	27 (25)	37 (11)

*FK 506 from August 1988 to February 1989, or cyclosporine from October 1987 to November 1988.

RESULTS

Patient and Graft Survival

Eight (7.3%) of the patients have died, leaving an actual survival of 92.7% after 6 to 12 months. The actuarial survival at 1 year is projected at 92% (Fig 1), which compares favorably with historical controls. Of the 102 survivors, 96 bear their original grafts, whereas 6 are surviving by virtue of a second (3 examples) or third graft (3 examples).

Retransplantation Rate

The consumption of grafts to treat these 110 patients was 124, meaning that the retransplant rate within 6 to 12 months was 12.7%. One hundred of the 110 patients were given a single graft, 6 were provided with two organs, and 4 patients had three organs. The factors necessitating retransplantation are summarized in Fig 2. Primary graft nonfunction, technical accidents, and rejection were the principal reasons for retransplantation. This profile was similar to that in the preceding era using conventional immunosuppression, although the absolute incidence was smaller in the FK 506 historical controls. As in the past, the need for retransplantation carried a degraded progno-

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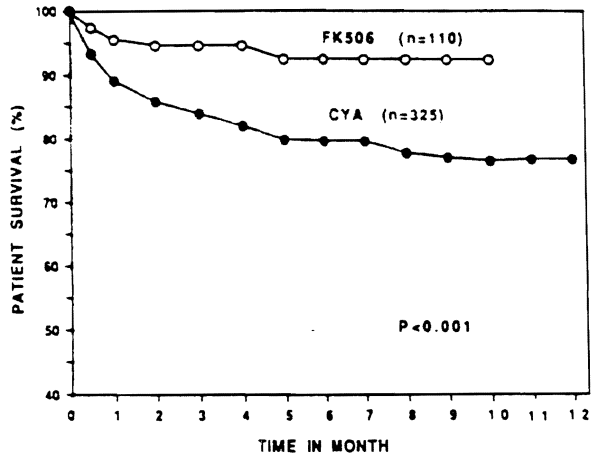

Fig 1. Patient survival curves in 110 consecutive adult liver recipients treated with FK 506, and 325 historical controls under conventional immunosuppression. Both series were consecutive, without culling for any reason including technical misadventures or primary graft dysfunction.

sis. Of the 10 patients who came to retransplantation during the 6- to 12-month follow-up period, only 6 (60%) survived.

Causes of Death

The causes of mortality in the whole series is summarized in Fig 3. In both the past and current experience, some of the deaths were caused by irreversible preexisting complications (for example, brain injury with fulminant hepatic failure), technical errors at the time of this complex operation, primary nonfunction of grafts, strokes, and heart failure. The principal improvement in mortality compared to the past was a reduction in complications of lethal infections (Fig 3).

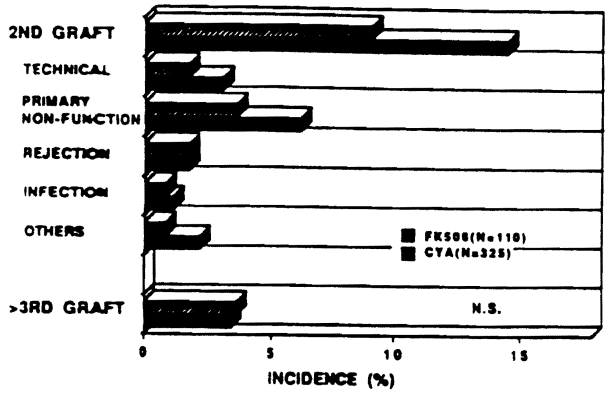

Fig 2. Incidence and cause of retransplantation within 6 months in FK 506 patients and in historical controls under conventional immunosuppression.

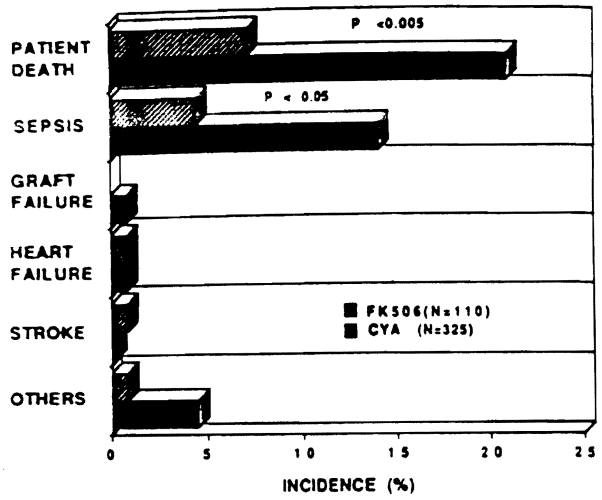

Fig 3. The incidence and cause of patient death in the first 6 months in the FK 506 patients and historical control patients treated with conventional immunosuppression. There have been no further deaths in the FK 506 patients, all of whom have been followed from 6 to 12 months.

Indices of Immunosuppression

Treatment during the first postoperative month with agents other than FK 506 and cyclosporine (CyA) is summarized in Fig 4 for the current and historical series. The amount of prednisone used for either bolus or maintenance treatment was greatly reduced in the FK 506 patients as was the administration of OKT3 and azathioprine. At the same time, the clinical diagnosis of rejection was made less frequently (Fig 4).

The steroid sparing was even more obvious as the months went by (Fig 5). Within 2 months, 45% of the FK

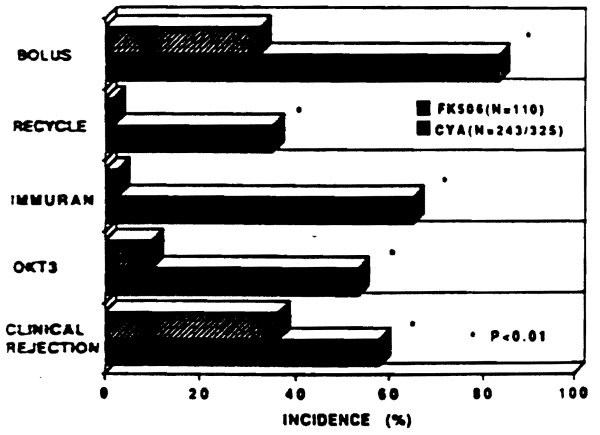

Fig 4. Other immunosuppressive agents used during the first postoperative month in all 110 adult patients treated with FK 506, compared to 243 historical control patients. Culled from the control group were recipients with catastrophic early courses, or those for whom information was incomplete because of early death and/or incomplete data retrieval.

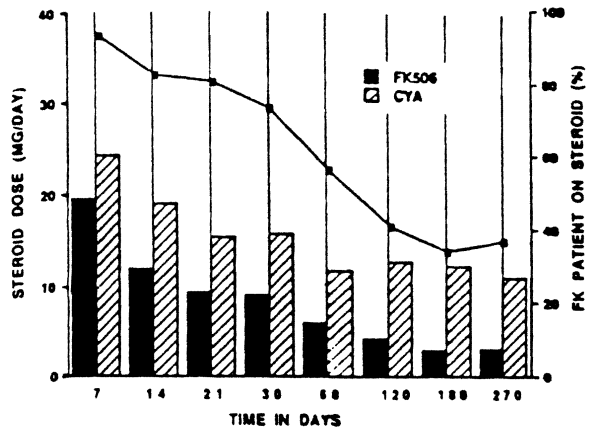

Fig 5. Average daily prednisone doses during the first 9 months. The data for the FK 506 and historical cases are complete out to 6 months, but partial for the 9-month FK 506 case entries since some of the later patients have not reached 9 months.

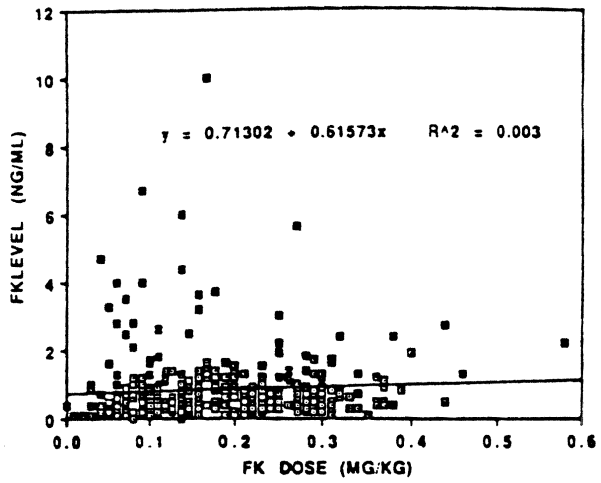

Fig 7. Although the doses and plasma FK 506 levels seem parallel in Fig 7, the correlation of doses and plasma levels in individual cases had no relationship.

506-treated patients were off steroids and throughout the first half-year further average reductions were possible (Fig 5).

The average FK 506 doses and plasma levels are shown in Fig 6. The starting IV dose was converted to the oral route in 90% of the cases within the first week. The plasma FK 506 levels were higher during the first 2 weeks than at any time later. After the patients were stable, the maintenance FK 506 levels were highly variable, and between 1 and 9 months there was no correlation in the plasma levels and the doses being given at the time of plasma testing (Fig 7).

In separate studies, the overriding effect of hepatic dysfunction on FK 506 pharmacokinetics has been described in detail.[6,7] In essence, the conclusion was that hepatic dysfunction disposed patients to overdosage when hepatic elimination was impaired, leading to toxicity and the need for highly individualized management. Because of this, the patients herein reported were stratified into 96 who had extended survival with relatively uncomplicated courses and 14 who received compromised grafts or failed to achieve good graft function for other reasons (Fig 8). After the perioperative period, those with smooth courses had very stable FK 506 doses and plasma levels with good liver graft function, and little or no permanent increase in serum creatinine. In contrast, the so-called compromised patients had higher and more volatile plasma FK 506 levels and concomitant significant elevations in serum creatinine (Fig 8).

Liver Function

The standard liver function tests in the foregoing 96 patients who were culled and stratified to the satisfactory group were compared to the best CyA cases. Culling of the 325 historical cases was more extensive, because there

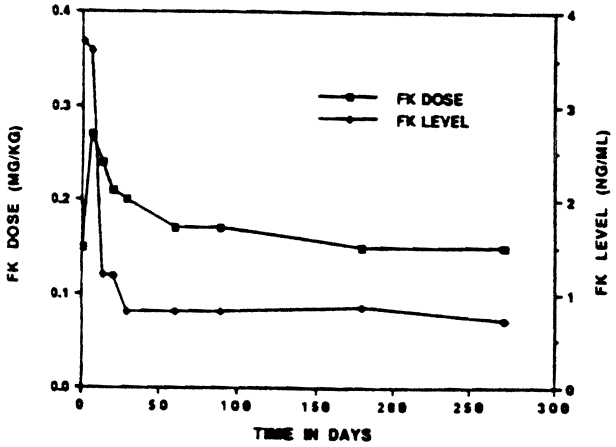

Fig 6. Daily doses of FK 506 in all 110 patients. Note the tendency of plasma FK 506 levels to be high early postoperatively.

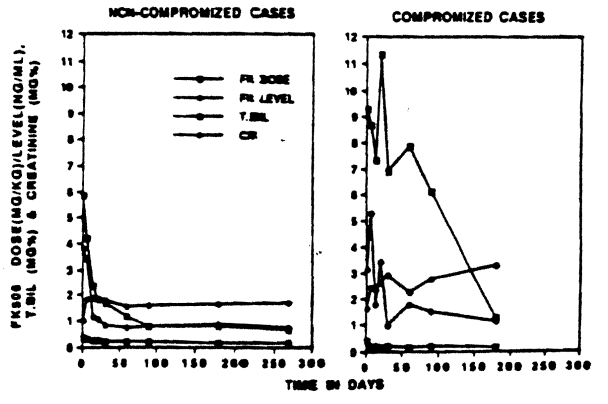

Fig 8. Stratification of patients into those with smooth courses (left) and those with difficult recovery. Note the slow resolution of jaundice, the higher plasma FK 506 blood levels, and the renal dysfunction that was reflected in elevated creatinines throughout.

Table 2. Cases Used for the Comparison of Hepatic and Renal Function Between FK 506 and Cyclosporine*

	FK 506	CyA
N	110	325
Primary OLTx		
n	100	259
Alive	96(87.3%)	193(59.4%)
Died	4	66
Multiple OLTx		
n	10	66
Alive	6	31
Died	4	35

*Followup period was 6–12 months in FK group, and 12 months in cyclosporine group.

were greater numbers of patients with early death or very difficult convalescence; 132/325 (40.6%) were eliminated, leaving 193 (Table 2).

The results of liver function in the current vs historical "clean" cases are shown in Figs 9–12 and showed no difference in the mean bilirubin, SGOT, SGPT, and gamma GTP values.

Renal Function

A significant rise in renal function during the first 5 postoperative months in the 11 compromised FK 506 recipients is shown in Fig 7. In the favorable FK 506 and historical series, there was no significant difference either in the early or late serum creatinine or BUN values, although there was a transient early increase in both (Figs 13, 14).

The patients treated with FK 506 had a low incidence of arterial hypertension (Fig 15). At the end of 6 months, only 22% were receiving some kind of antihypertensive medication, in almost all instances with a single drug. Many of these patients were hypertensive preoperatively. McCauley et al[8] are reporting a complete analysis of these cases

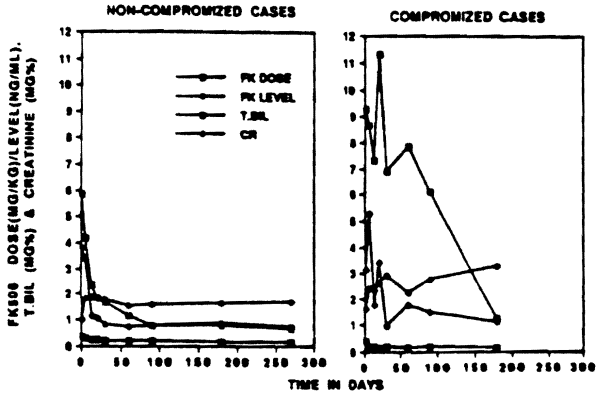

Fig 9. Average serum bilirubin concentrations in the 96 FK 506 patients with smooth courses shown in Fig 8, in comparison to the bilirubins in 193 similar patients treated with a cyclosporine-containing regimen.

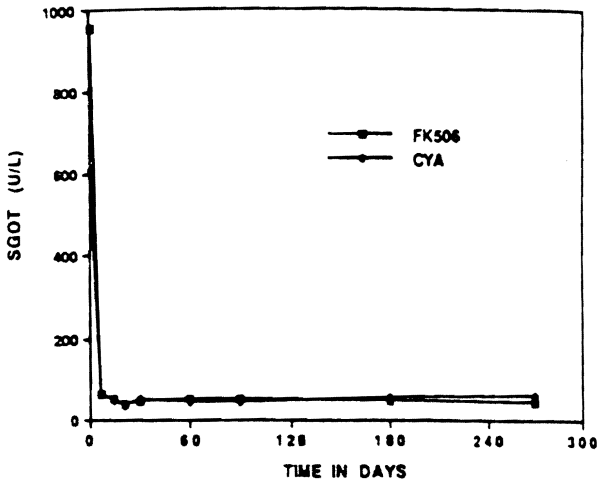

Fig 10. SGOT values in same comparison as in Fig 9.

elsewhere at this meeting with special focus on those who had continuous function of their first liver graft.

Other Measurements

The serum cholesterol values became stable at a normal range within 2 months (Fig 16). There was no identifiable upward drift. Uric acid values were normal initially, but with a tendency for a later average increase. The significance of these findings is under study.

DISCUSSION

The information reported herein was similar to that in an earlier report[4] but with 4½ months longer follow-up. What has accrued is further evidence of the feasibility and safety of both acute and chronic treatment with FK 506. No patient entered into the study has been removed from it. With follow-up of 6 to 12 months, we are able to project accurately that patient survival will be at 90% or higher with the graft survival not far behind. This has been better

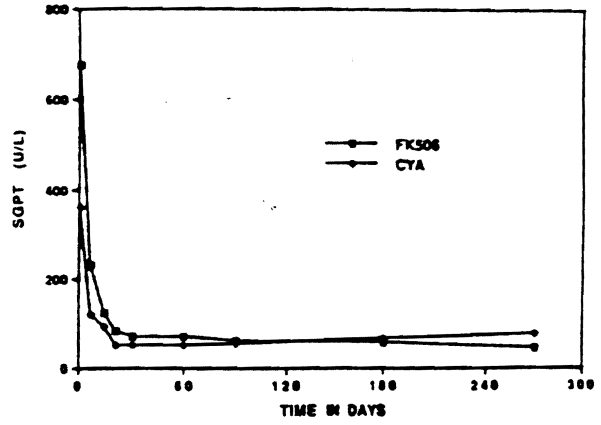

Fig 11. SGPT values in same comparison as in Fig 9.

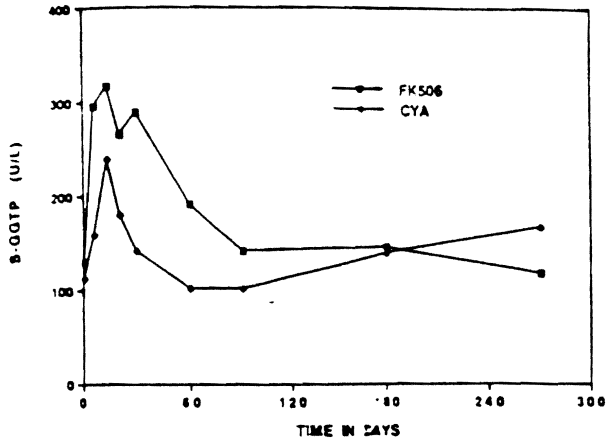

Fig 12. Serum gamma glutamyl transpeptidase (S-GGTP) in same comparison as in Fig 9.

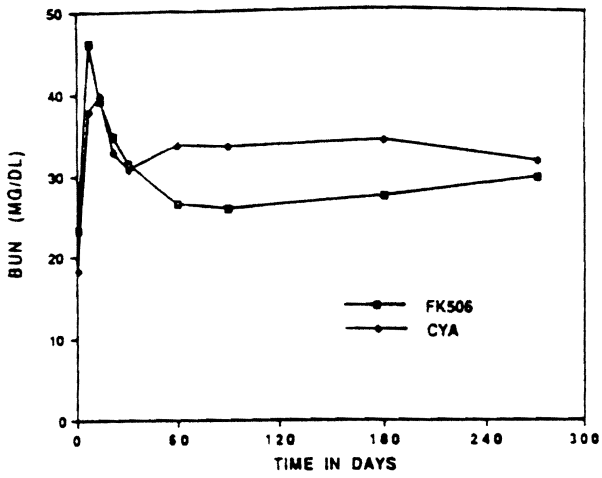

Fig 14. Average blood urea nitrogen values (BUN) in the FK 506 and cyclosporine patients shown in Fig 9.

than we were able to achieve previously with the same or more favorable case mix.

The incidence of nephrotoxicity and other side effects has been acceptable, and largely confined to patients (about 11% of the total) who were classified as compromised by poor hepatic graft function, or by catastrophic technical or metabolic complications. A relative freedom from arterial hypertension was noteworthy under FK 506. The general characteristics of the surviving patient population in terms of liver function were no different from that in patients who had a smooth recovery under CyA, but this was achieved with very low steroid requirements.

These results were from a pilot trial in which no preliminary groping for the optimal management policies was involved, and, consequently, every case of primary liver transplantation including the first one contributed to the series. As discussed elsewhere,[6,7] the induction doses of FK 506 may have been higher than necessary or desirable, particularly if good immediate graft function was not achieved. However, what was learned justifies further examination of this drug's potential, not only in liver transplantation but also in transplantation of other organs and for nontransplant indications.

There can be little argument against the next stage of randomized trials on grounds that FK 506 may be an inferior drug. Rather, the ethical dilemma could be the obverse, that there is considerable evidence already that FK 506 regimens provide the best chance for patient survival. The dilemma has been made particularly troubling by the demonstration that FK 506 can be used as a court of last appeal in liver and heart recipients, when all other conventional approaches have already failed.[2,5,9]

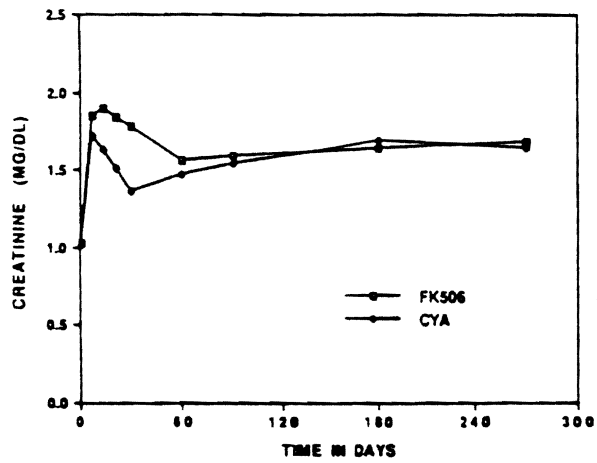

Fig 13. Average serum creatinine values in the FK 506 and cyclosporine patients shown in Fig 9.

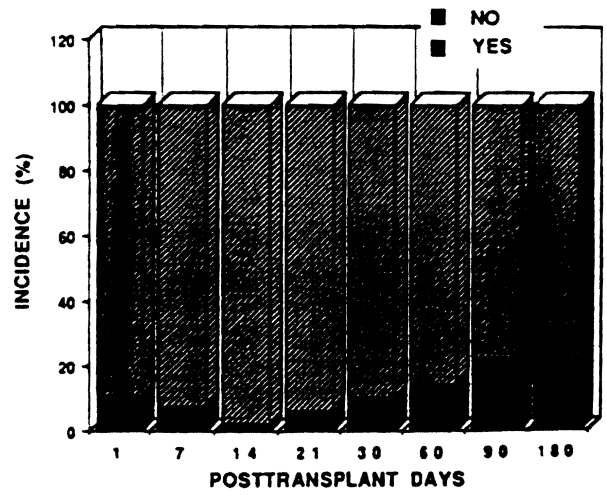

Fig 15. Need for antihypertensive in 102 patients who survived for the first 6 months under FK 506 immunosuppression. Almost all of those receiving an hypertensive medication were on a single drug.

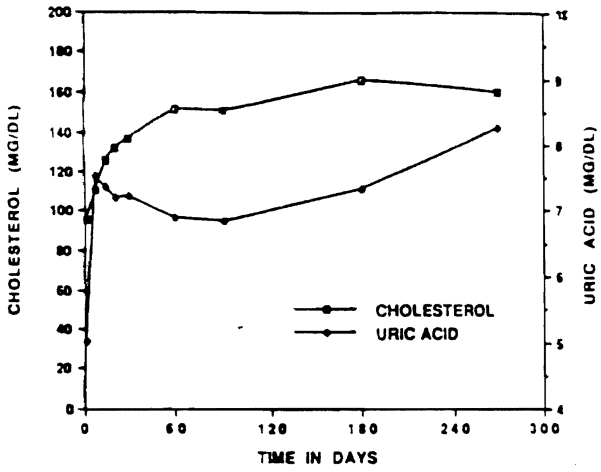

Fig 16. The course of serum cholesterol and uric acid levels after liver transplantation under FK 506.

SUMMARY

An account is given of the 6- to 12-month survival, and causes of failure in 110 consecutive patients who underwent primary liver transplantation under treatment from the outset with FK 506 and steroids. The patient survival is 92.7%, and the first graft survival is 87.3%. At a very high frequency, the patients achieved good graft function, and they had a relatively low morbidity that was partially ascribable to minimal use and early discontinuance (in 60% of cases) of steroids. Renal dysfunction and other adverse findings were largely confined to patients with poor initial graft function and consequent apparent alteration of the kinetics of FK 506 elimination, causing functional overdosage. Results compare very favorably with our past record using conventional immunosuppression, and support the belief that FK 506 is a superior immunosuppressive agent which is suitable for chronic administration.

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