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A Randomized Trial of Primary Liver Transplantation Under Immunosuppression With FK 506 vs Cyclosporine

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We have reported encouraging clinical trials with a new immunosuppressive agent called FK 506,[1-3] which is a macrolide antibiotic produced by the fungus *Streptomyces tsukubaensis*.[4] The molecular structure of FK 506 is unrelated to cyclosporine (CyA), and the two drugs have different cytosolic binding sites.[5,6] However, both drugs inhibit T-lymphocyte activation, in part by suppressing the synthesis and expression of the cytokine interleukin 2.[4,7,8] Both drugs appear to be potent suppressors of T-cell function, although FK 506 accomplishes equal immunosuppression at levels 100 times less than that of CyA. The first clinical use of FK 506 was preceded by extensive in vitro and in vivo studies.

In the first human studies with FK 506, this agent was used as a "rescue" drug, in that patients with complications and failure of CyA were converted to FK 506. The results of this study showed a marked ability to reverse ongoing rejection, even in cases where chronic changes were observed.[1,3] This served as the rationale to begin trials of FK 506, with low-dose steroids, as the initial immunosuppressive regimen to treat liver transplant patients. This Phase I primary treatment study was begun on August 16, 1989. These were the first human patients to be given FK 506, along with low-dose steroids, as their primary immunosuppressive baseline regimen. FK 506 was shown to be remarkably potent and successful as primary immunosuppression in liver transplantation. Detailed analysis of the results of the FK 506 primary treated liver allograft recipient group has been reported. There were 110 adult patients entered at the Presbyterian University Hospital up to February 4, 1990. In comparison, a total of 320 consecutive liver transplant patients treated with CyA in 1988 were used as a historical control group. Ninety-nine (90.0%) of the 110 FK 506 primarily treated liver transplant patients were alive at 12 months following transplantation, with a corresponding graft survival of 83%. These foregoing results were statistically better than that of the CyA-treated control group.

The next phase of FK 506 study, which sequentially followed the initial pilot study, was to perform a randomized trail to compare FK 506 with CyA. The design of this study was to use FK 506 and CyA, along with steroids, in a randomized fashion in patients undergoing primary liver transplantation. Patients with significant preoperative risk factors were excluded from randomization because of a high risk of development of posttransplant medical problems.

The primary endpoint of the randomized study was the failure of a defined treatment regimen to prevent and control rejection. Our initial presumption was that graft and patient survival would be essentially the same between the two treatment groups because patient outcome after

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treatment failure was individualized to each patient as deemed necessary by the investigators. Therefore both patient and graft survival were considered only as a secondary endpoint. The degree of freedom from rejection was considered a parameter associated with the primary endpoint, and this figure was also analyzed between the two groups. Freedom from rejection and requirement of supplemental immunosuppression were chosen as primary endpoints to provide sufficient objective evidence to resolve key questions, while preserving, as much as possible, the ethical responsibility to treat patients in accordance with the best practice, as currently understood.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

All male and female patients 16 to 60 years of age who were referred for liver transplantation were considered as potential candidates for randomization, with appropriate informed consent. The following patients were excluded from randomization if they met any of the following criteria:

1. Hepatitis B virus carriers
2. Patients with cancer
3. Patients undergoing multiple organ transplantation
4. Patients with pre-existing renal failure
5. Active infection
6. Stage 4 coma, defined as unconscious and ventilator dependent
7. Clinically significant heart or lung disease
8. Previous reconstructive or bypass procedures of the liver
9. Technically unsatisfactory operations with poor immediate liver function.

Details of Randomization

The patients were randomized 4 hours after full revascularization, shortly before the first dosage of FK 506 or CyA was administered. The surgeons did not know the randomization status during the donor search, operation, or early intraoperative phase. Treatment assignment was determined by a computer program implementing the block randomization technique, to assure that the treatment groups remained reasonably balanced. A sealed envelope method was implemented. Each envelope contained a single treatment assignment.

Immunosuppressive Therapy

FK 506—An intravenous dose of 0.10 mg/kg of FK 506 was administered over a period of 24 hours, beginning 4 hours alter the new liver was revascularized, and continued daily until patients were able to take oral medications. At this time, 0.15 mg/kg was given orally every 12 hours. Provisions to either increase or reduce the oral dose were made, if adequate levels of FK 506 were not maintained, as judged by the clinical course and FK 506 blood levels. Twelve-hour levels were monitored and levels of 1.0 ng/mL–5.0 ng/mL maintained. FK 506 doses were increased if there was evidence of rejection and there was little or no associated toxicity at the present dose, and if FK 506 oral trough levels were not above 5 ng/mL. Trough plasma levels of FK 506 were measured by a monoclonal enzyme immunoassay technique.[9]

Cyclasponne (CyA)—An intravenous dose of 4 mg/kg of CyA was administered over a period of 24 hours, beginning 4 hours after the new liver was revascularized, until patients

were able to take oral medications, at which time CyA doses of 8 mg/kg were given orally every 12 hours. Again, provisions to increase the oral dose were made if adequate levels of CyA were not maintained and to reduce the dose if indicated by CyA whole blood levels and/or CyA toxicity. Tdx CyA levels of 800 to 1500 ng/mL were maintained on 12-hour trough levels. Allowance for downward TdX CyA trough levels were made during the 2nd postoperative month to 600–800 ng/mL. CyA doses were increased if there was evidence of rejection and there was little or no associated toxicity at the present dose, and if TdX CyA blood levels did not rise above the 1500 ng/mL range.

Steroid Therapy—For both treatment groups, a single intraoperative dose of 1 g of intravenous methylprednisolone was given followed by a daily dose of 20 mg/d until oral therapy was started. A dose of 20 mg/d of prednisone was given once oral medications were started. A dose reduction to 10 mg/day was allowed, with both FK 506- and CyA-treated patients, at 2 weeks if there had been no evidence of clinical or histopathologic rejection. A further dose reduction to 5 mg/d was allowed at the end of the month if there had been no evidence of rejection. Patients were taken otf steroids if there was no evidence of rejection.

Supplemental Immunosuppression

In the event of liver allograft dysfunction, a liver biopsy was obtained and evaluated in a blinded manner by the liver transplant pathologists, without knowledge of the treatment group. One gram of intravenous methylprednisolone was given for biopsy-proven rejection. If no response was obtained within 48 hours, or if worsening of biochemical parameters or clinical deterioration occurred, then the endpoint had been reached and this event was recorded and treatment was individualized. If a patient was randomized to receive CyA, then failure of supplemental steroid was treated either by conversion of the baseline immunosuppression from CyA to FK 506, or by a 5-day course of OKT3 (10 mg/d), or further augmentation of steroids. If a patient was randomized to receive FK 506, then the steroid-resistant rejection episode was treated by a 5-day course of OKT3, or by augmentation of steroids. Response was defined as the return of the abnormal parameter to the baseline value.

Definition of Liver Rejection

The diagnosis of liver allograft rejection was based on the positive histologic findings but also required preliminary negative studies as follows: liver ultrasound with intact liver vascularization, and non-dilated bile ducts. A cholangiogram and an arteriogram were performed if the ultrasound findings were equivocal.

Clinical findings that suggest rejection were based on clinic biochemical, and pathologic[10] features. These features include the following:

Clinical: fever >38.3°C, without a source of infection; diminished bile output or altered bile character if a T-tube was present: and/or presence of increased ascites.

Biochemical: elevation in total bilirubin, SGOT, SGPT, alkaline phosphatase and/or gamma-glutamyl transpeptidase 1.5 times the larger value of either the lowest value I week prior to onset of liver dysfunction, or over the upper limit of normal.

Pathological:

a. a predominantly mononuclear portal tract infiltrate in which the inflammatory infiltrate consisted of 50% to 60% mononuclear cells intermixed with polymorphonuclear cells and eosinophils;

b. characteristic localization of the inflammatory cells around and beneath the swollen endothelium of portal capillary and small veins, with infiltration and damage of the epithilium of small bile ductules;

c. absence of the following histologic findings: significant panlobular inflammation; piecemeal necrosis; cholangiolar proliferation; disarray, with ballooning and spotty individual hepatocyte necrosis; and prominent lymphohistiocytic infiltration of the hepatic lobule, with inflammatory cell destruction of hepatocytes.

Statistical Analysis

Comparison of the two treatment arms, in regard to patient survival, used Kaplan Meter estimates. Graft survival and freedom from rejection were treated similarly. Patients who died with an apparently functioning graft were treated as graft failure so as to obviate the need to decide the cause of death in each case. Statistical comparisons of both graft and patient survivals were made utilizing the Peto-Prentice method.

Adjustments for prognostic factors, using proportional hazard modeling, was not utilized in this analysis. In this randomized trial, most adverse prognostic factors affecting liver transplantation, were eliminated by the exclusion criteria. These patients were excluded from randomization because of a high risk of development of posttransplant medical problems that may affect graft and patient survival.

RESULTS

Patient Profiles

Eighty-one patients were entered into randomization during the period of February 17, 1990, to August 31, 1990. Follow-up of all patients was to May 7, 1991. Forty-one patients were randomized to receive FK 506 following liver transplantation, while 40 patients were randomized to the CyA group. Table 1 shows the clinical data of patients randomized to the CyA and FK 506 treatment groups. The median follow-up for both groups was the same, 346 days for CyA and 343 days for FK 506. The median age for both groups was 42 years of age. The male/female ratio was slightly skewed in the CyA group (27 males, 13 females), whereas the FK 506 group was about equal (21 males, 20 females). The incidence of the original liver diseases, with respect to biliary cirrhosis vs hepatocellular disease, was similar in both groups. Biliary cirrhosis accounted for 10 patients in the FK 506 group and 7 patients in the CyA group. Hepatocellular disease accounted for 31 patients in the FK 506 group and 33 patients in the CyA group.

Patient and Graft Survival

Patient death was defined as patient death (from any cause), while graft failure was defined as patient death or graft replacement. Fig 1 depicts the patient survival curves for the 41 FK 506 and 40 CyA randomized patients. The 3-month patient survival for the two groups was 100% for the FK 506 patients and 90% for the CyA group. The 6-month figures for patient survival were 95% and 85%, respectively ($P = .400$, NS). The 12-month patient survival for FK 506 and CyA groups was 93% and 81%. respectively ($P = .18$, NS). Fig 2 illustrates the corresponding graft survival curves for these patients. The 3-month graft survival for the two groups was 95% for the FK 506 vs 83% for the CyA group. The corresponding 6-momh figures were 93% and 78%, whereas the 12-month graft survival was 90% and 70%, respectively.

The causes of patient and graft losses are also listed in Table 1. In the FK 506 group, three patients died, two from sepsis (one bacterial, one opportunistic fungal), and one from an iatrogenic cause (hemothorax). In the CyA group, seven patients died. One patient died as a

sequela of rejection, developing hemodynamic instability before re-transplantation could be performed. Two patients died from bacterial sepsis, following retransplantation for vascular thrombosis preceded by rejection. One death was attributed to disseminated posttransplant lymphoproliferative disease (PTLD) after conversion to FK 506 following rejection. One death was attributable to complications related to respiratory arrest following retransplantation for preservation injury. One patient died because of overwhelming sepsis related to neutropenia following treatment for cytomegalovirus infection following conversion to FK 506. One other patient died as a result of *Pneumocystis carinii* infection, 8 months following transplantation.

Two patients in the FK 506 limb required retransplantation. one from cytomegalovirus infection and the other from a combination of rejection and ischemic injury. Seven of the original CyA-treated liver allografts were retransplanted. Three grafts were lost to rejection or complications of rejection and were retransplanted. Two grafts suffered severe ischemic injury and required retransplantation. One graft was retransplanted because of persistent hemolysis related to Rh incompatibility. One liver was lost at 350 days because of hepatic artery thrombosis and accelerated graft atherosclerosis.

Incidence of Rejection

One measure of the effectiveness of a baseline immunosuppressive regimen is the rejection-free rate following transplantation. Because liver allograft rejection was strictly defined biochemically, histologically, and/or clinically, this parameter was a simple, objective endpoint. A total of seven CyA patients were excluded from this analysis, leaving a total of 33 liver allografts that could be evaluated for development of rejection. Two patients in the CyA group were retransplanted because of persistent preservation injury: one patient requested removal from CyA and conversion to FK 506: and one patient was retransplanted because of Rh incompatibility with hemolysis. Three additional grafts were converted from CyA to FK 506 early in the posttransplant period because of an element of ischemic injury. No patient in the FK 506 group was excluded in this analysis.

Fig 3 shows the percentage of patients in each group who remained rejection free. The major incidence of rejection episodes in both groups occurred within the first 30 days. In the FK 506 group, the first episode of rejection occurred at a mean day of 21.5 following transplantation. In contrast, the first rejection episode occurred a mean of 9.9 days following transplantation in the CyA group $P < .005$). In addition, a statistically significant larger number of patients in the FK 506 group remained free of rejection during the period of follow-up ($P < .025$). At 1 month, the rejection-free rate for the FK 506 patients was 61.0%, while the CyA value was 18.1% ($P < .001$). There were few late rejections, three in the FK 506 group over the next 11 months, while two additional late rejections were seen in the CyA group.

Supplementation of Immunosuppression

Augmented immunosuppression was used when the standard immunosuppressive regimen was unable to control rejection. The initial treatment was a bolus of methylprednisolone to reverse an episode of liver allograft rejection. When the augmented steroid dose was unable to reverse the rejection, subsequent treatment was individualized in all instances. FK 506 crossover, administration of a steroid recycle, or administration of OKT3 were options in those patients on CyA. On the other hand, patients on FK 506 were given OKT3 or additional steroids. The mean number of steroid boluses given per patient during the first 90 days was 0.50 for the FK 506 group and 0.99 for the CyA group ($P < .01$).

In the FK 506 group, a total of eight patients (8/41, 19.5%) required OKT3. Only one patient related to failure of FK 506 required retransplantation with OKT3. This patient also had evidence of persistent preservation injury.

In the CyA group, a total of 12 patients (12/40, 30%) required OKT3. A total of 29/40 CyA-treated patients were convened to FK 506. The reasons for CyA conversion to FK 506 are shown in Table 2. Of the 12 CyA patients who required OKT3 related to ongoing rejection, a total of eight patients were converted to FK 506 after a course of OKT3. Twelve additional patients were converted to FK 506 following failure of a course of augmented steroids, without utilizing OKT3. Two other patients were converted to FK 506 as primary therapy tor rejection, one because of difficulties in the control of diabetes, and the other patient who refused additional steroids. Five CyA-treated grafts were converted to FK 506 because of persistent ischemic changes in the immediate posttransplant period, and one because of dropout from the CyA group related to patient request. Of the five grafts converted to FK 506 for ischemic injury, two required retransplantation, while three grafts improved. One patient was given a course of steroids, OKT3, and finally converted to FK 506, because of an Rh incompatibility, which eventually required retransplantation.

Renal Function

Renal function in both groups of patients was assessed by the requirement for hemodialysis and the serum creatinine at monthly determinations. The requirement for hemodialysis, as a preterminal event, was seen in one patient in the FK 506 group, and in three patients in the CyA group. Hemodialysis was initiated in six CyA patients while still on CyA, whereas three other CyA patients required hemodialysis during the period of conversion to FK 506. In the FK 506 randomized group, four patients were placed on hemodialysis during the posttransplant period. The comparative incidence for hemodialysis requirement between the FK 506 and CyA groups (excluding terminal hemodialysis) was 10% and 21.6%, respectively. Long-term hemodialysis (after 3 months' posttransplant) was only required in one patient in each group.

Table 3 shows the mean serum creatinine of patients with functioning kidneys, each month following transplantation, for both FK 506 and CyA patients. In addition, those patients who were converted to FK 506 from the CyA group have creatinine levels shown separately. During the first 4 months there was little appreciable difference in the serum creatinine for the three groups with functioning kidneys.

Infectious Disease and Malignant Complications

Incidence of opportunistic infections was analyzed for each patient, with appropriate investigations when clinically indicated, and with routine surveillance cultures for viral infections. The incidence of opportunistic infections was essentially the same for both groups. Patients who were randomized to CyA had a 22.5% incidence of cytomegalovirus infections (CMV). This compared to 22.0% incidence for patients on FK 506. In the 13 CyA patients who were not switched to FK 506, the incidence of CMV was 23% (3/13), and only one of the three patients received OKT3. In the FK 506 patients, three of the total nine cases of CMV occurred in patients who had previously received OKT3.

Two cases of miliary tuberculosis were seen in patients originally randomized to CyA but switched to FK 506 after having received augmented steroids and OKT3. Both patients responded to triple drug therapy with rifampin, isoniazid, and ethambutol. Single cases of recurrent hepatitis C virus, acquired hepatitis B, and herpes simplex virus were seen in the CyA-treated group. In addition. three cases of severe symptomatic candidal infections were seen in this group. Two cases of PTLD were seen in the CyA randomized patients. One occurred in a patient who was converted to FK 506 for steroid-resistant rejection, whereas the other occurred in a patient who was still on CyA.

In the FK 506-treated group, there were two cases of recurrent hepatitis C virus and one case of acute mononucleosis due to Epstein-Barr virus. One fatal case of disseminated Candida was

seen in a patient who did not require any augmented immunosuppression while on FK 506 therapy.

Other Parameters

Hypertension—The severity of hypertension was assessed by the need for antihypertensive medications following transplantation. The incidence of hypertension in the overall CyA randomized group was 52.9% vs 26.9% for the FK 506-treated group ($P < .01$), at 3 months' posttransplant. This figure did not change appreciably over the follow-up period; at the current follow-up period, the corresponding hypertensive incidence was 48% for CyA and 33.3% for FK 506. The incidence of hypertension in the 14 patients who were on CyA at the 3-month posttransplant period was 64.2%. The current figure (at the time of analysis) was 72.7% for those patients still on CyA, while the conversion group had an incidence similar to those given FK 506 from the start (36.4%).

Induction of Diabetes Mellitus in Nondiabetic Patients—The need for insulin therapy was evaluated by determining those patients who required insulin at the 3-month period following transplantation. No statistically significant differences existed between the two groups of patients. In the FK 506 group, 17% of the patients required insulin at 3 months' posttransplant. For the CyA group, 17.5% of the patients required insulin at the same time point.

Prednisone Requirements—The amount of maintenance prednisone required to maintain graft stability was determined at monthly intervals. As shown in Fig 4, the mean maintenance dose of methylprednisolone was lower for the FK 506 patients and the FK 506-converted CyA patients, than it was for the CyA-mamtained group.

Other Adverse Reactions—Both FK 506 and CyA administration have been associated with side effects, many of which are similar. The percentages and severity of patients experiencing treatment-related adverse reactions were recorded. This included evidence of neurotoxicity: trembling, paresthesias, insomnia, irritability, hyperkinetic behavior, dysarthria, seizures, and coma. As can be seen in Table 4, the incidence of side effects was essentially the same between both groups.

CONCLUSIONS

This trial provided a unique opportunity to compare the conventional CyA treatment of liver transplant recipients with a drug (FK 506) that is more potent than CyA. By performing a randomized trial, a more complete determination of its advantages and limitations relative to those of CyA therapy could be ascertained. From this analysis, it appears that FK 506 is at least as effective as CyA, and that, in certain aspects, FK 506 may be superior to CyA. Other parameters, such as freedom from rejection, incidence of hypertension, and use of steroids, appear statistically better with FK 506 than with CyA. These benefits do not appear to be at the expense of increased incidence of renal failure, infectious complications, tendency to develop diabetes mellitus, or other major side effects.

The potency of FK 506 as an immunosuppressive agent has been previously demonstrated. Both CyA and FK 506 bind to a family of *cis-trans* peptidyl prolyl isomerases.[5,6] Characterization of the effect of these agents on intracellular processes, such as calcium-dependent pathways, and the effect on cytokine expression suggest a differential effect by CyA and FK 506. The relative similarity of both agents on infectious complications probably relates more to factors such as the CMV status of the donor and recipient as well as to technical complications, rather than to an enhanced immunosuppressive quality of either agent. In fact,

FK 506 has been shown to diminish NK cell activity to a less degree than CyA.[11] The incidence of posttranspiant lymphoproliferative disease with FK 506 has been 1.9%, similar to that seen with CyA.[12]

The relative susceptibility of liver transplant recipients to nephrotoxicity also relates to perioperative risk factors, such as use of nephrotoxic antibiotics, perioperative hypotension, and preexisting renal dysfunction. Tauxe and coworkers have shown that candidates awaiting liver transplantation have a significant preexisting decrement in renal function, as manifested by a 35% decrease in estimated renal plasma flow and a 15% decrease in the glomerular filtration rate (privileged communication). Nevertheless, FK 506 and CyA can affect renal function by increasing renal vasoconstriction, perhaps by increasing endothelin-I secretion (R. Yatscoff, personal communication). The overall cumulative incidence of renal dysfunction, manifested by elevation in serum creatinine, has been reported in about 70% of all FK 506 liver transplant patients, usually during the first 2 posttranspiant days.[13] Both drugs are associated with an increase in the development of insulin-dependent diabetes mellitus, by increasing the peripheral resistance to insulin, and by diminishing the insulin release by islet cells perhaps by inhibition of synexin-mediated exocytosis of islet cell granules.14

Results of the current randomized study compare favorably to previously reported results using FK 506 and therefore do not appear to represent a bias in the performance of the study. It is important that the results of the current ongoing randomized trial are comparable to those results obtained in the historical series. The current results of patient and graft survival are as good, if not better, than those figures obtained in the past. One would expect that both graft and patient survival would be better in the randomized trial, since the high-risk patients are removed from randomization. The randomized FK 506 liver patients were compared to the survival curves of 271 nonrandomized FK 506 recipients and 813 CyA recipients during the period of time corresponding to the utilization of Viaspan (Dupont). The 1-year patient survival for the high-risk FK 506 liver recipients not entered in the randomized trial approaches 82%, while graft survival is 76%. This compares to our historic CyA patient and graft survival of 77% and 68%, respectively. The improvement of the current randomized CyA group over the historic CyA group may in part be related to the ability to convert patients on CyA to FK 506.

Ever since the initial enrollment of the 81 patients reported in this series, a modification of the baseline immunosuppression for the CyA limb has been initiated. Treatment of the CyA limb with higher-dose steroids and inclusion of steroid recycle at the time of transplantation and as part of the treatment of rejection has been implemented. A total of 20 additional CyA patients have been enrolled. The preliminary analysis does not greatly alter the findings reported in this study. The percentage of patients who are rejection free using augmented steroids in the CyA group is 23% at 6 months, while the corresponding incidence for FK 506-treated patients is 44% at the same period, although the percentage of patients who have been converted from CyA to FK 506 is lower at 54%.

Ongoing prospective randomized trials of CyA vs FK 506 for primary liver transplantation are also underway in multicenter trials in the United States and in Europe. More stringent criteria for conversion of CyA-treated patients to FK 506 will allow one to evaluate the impact of CyA and FK 506 immunosuppression on primary endpoints including patient and graft survival.

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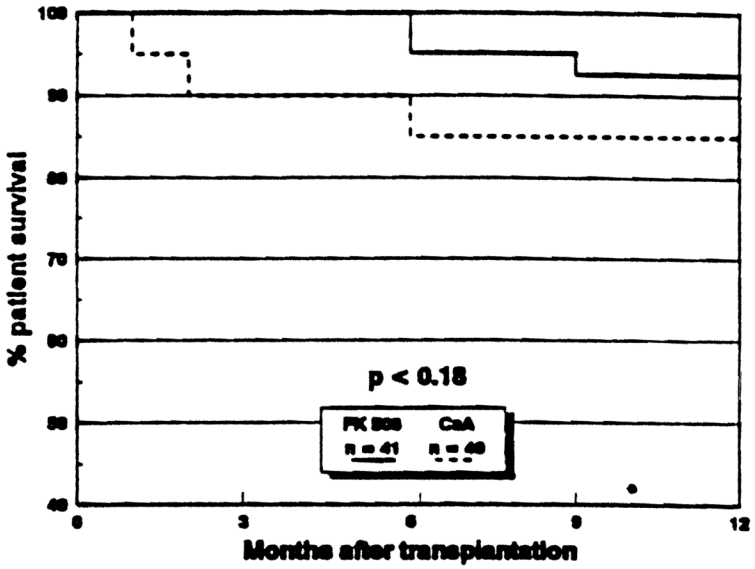

Fig 1.
Comparison of the patient survival curves for all FK 506- and CyA-randomized patients.

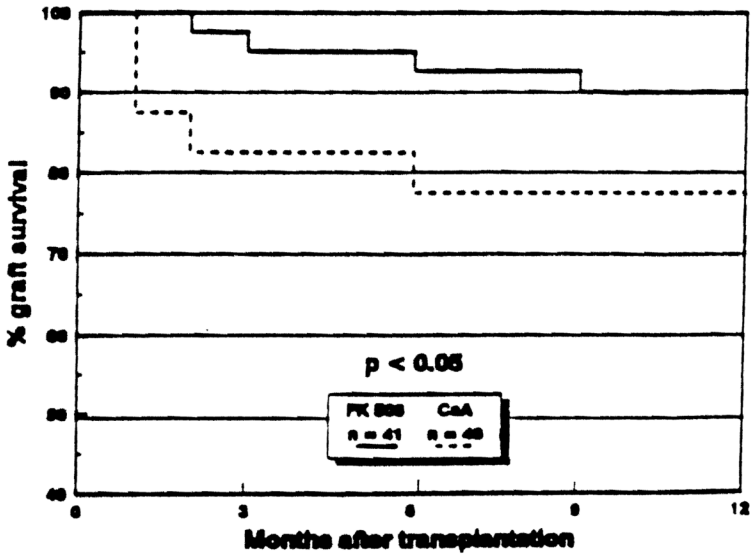

Fig 2.
Comparison of the graft survival for the original FK 506- and CyA-ranoomized liver allografts.

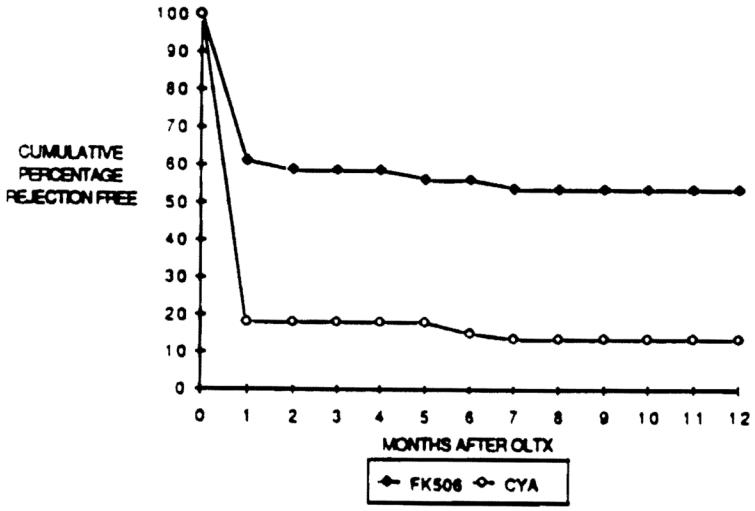

Fig 3.

The percentage of patients in each group who remained rejection free is plotted against the number of months posttransplant for both CyA and FK 506 patients.

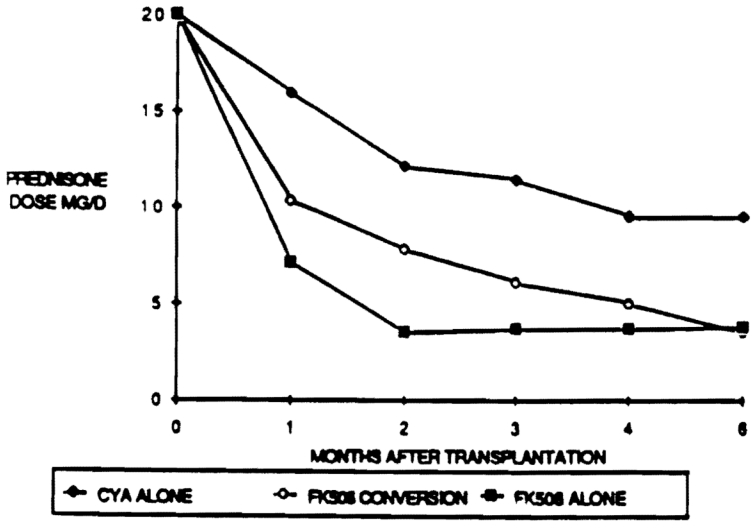

Fig 4.

The mean doses of prednisone per day is charted against the time posttranspiant for CyA and FK 506 groups. For the CyA group, two curves are shown, one being for those patients who still remain on CyA vs the group that was converted to FK 506. The percentage of patients in each group who are off all steroids is shown at each time point.

Table 1

Patient Characteristics

	FK 506	CyA
Number of patients	41	40
Median age (y)	42	42
Median follow-up (d)	343	346
Male/female	21/20	27/13
Original liver disease		
Biliary cirrhosis	10	7
Hepatocellular	31	33
Number of deaths	3	7
Causes of death		
Infection	2	3
Rejection	0	1
Malignancy	0	1
Other	1	2
Number of retransplantations	2	7
Causes of retransplantation		
Infection	1	0
Rejection	1	3
Preservation injury	0	2
Other	0	2

Table 2

FK 506 Conversion in CyA Patients*

Causes	No.
Rejection	22†
OKT3 failure	8
Primary rejection therapy	2
Steroid failure	12
Preservation injury	5
Retransplantation	2
Rh incompatibility	1
Patient dropout from CyA limb	1

*Total number of CyA to FK 506 conversions = 29.

†Includes three patients who were converted to FK 506 at the time of retransplantation for rejection.

Table 3

Serum Creatinine in CyA and FK 506 Randomized Patients

Post-OLTX Month	CR (mg/dL)
CyA—Not converted	
1	1.53 ± 0.39
2	1.59 ± 0.39
3	1.66 ± 0.41
4	1.71 ± 0.32
6	1.68 ± 0.44
CyA—FK 506 rescue	
1	1.71 ± 1.17
2	1.90 ± 0.51
3	2.06 ± 0.84
4	1.62 ± 0.67
6	1.61 ± 0.69
FK 506	
1	1.54 ± 0.62
2	1.70 ± 0.61
3	1.71 ± 0.70
4	1.61 ± 0.41
6	1.75 ± 0.71

Table 4

Incidence of Side Effects

	Incidence	
Side Effect	**CyA (%)**	**FK 506 (%)**
Blurred vision	13.1	13.2
Chest pain	2.2	3.7
Decreased appetite	8.8	9.9
Diarrhea	12.8	11.7
Dizziness	5.9	4.6
Fatigue	8.8	12
Gas pain	16.3	16.2
Hair growth	14.1	5.2
Hair loss	7.5	10.1
Headache	16.3	23.7
Hyperesthesia	28.5	21.3
Musculoskeletal	26.7	20.6
Increased appetite	7.2	8.3
Insomnia	28.5	41
Nausea	6.7	8.3
Nightmares	2.8	5.0
Photophobia	11.7	10.7
Pruritis	10.7	10.4
Shortness of breath	5.0	5.5
Sweating	6.1	7.7
Tinnitus	11.2	6.4
Tremors	24.0	24.0