Liver Transplantation of American Veterans Under FK 506
Immunosuppression: A Preliminary Report


During the cyclosporine (CyA) era, results of liver transplantation in American veterans were worse than those obtained in the private sector. Encouraged with our initial experience at the University of Pittsburgh, a trial of liver transplantation under FK 506 was initiated at the Pittsburgh Veterans Affairs Medical Center (PVAMC), with the expectation of improving results in this group of patients.

Materials and Methods
Patient Population
From October 22, 1989 to April 17, 1991, a total of 29 consecutive liver transplants were performed in 27 patients under FK 506 and steroid immunosuppression. The minimal follow-up was 30 days in all surviving patients. Patient demographics and indications for liver transplantation are shown in Table I. Other characteristics of the group disclosed in Table I include: the United Network for Organ Sharing (UNOS) classification, the presence of previous abdominal surgery, and the number of patients with portal vein thrombosis and/or sclerosis requiring iliac vein grafts.

Immunosuppression
FK 506. The first seven patients received 0.15 mg/kg of FK 506 IV over 4 hours, and then 0.075 mg/kg IV every 12 hours until able to take oral medications. The remaining 20 patients received 0.10 mg/kg as a continuous drip over 24 hours, again, until able to take oral medications. The oral dose in both groups was 0.15 mg/kg every 12 hours. Dose adjustments were made according to the clinical course, with the aim of maintaining trough levels between 1 and 2 ng/mL during the first weeks after transplantation.

Steroids. All patients received 1 g of methylprednisolone immediately after revascularization of the graft. In the first seven patients this was followed by a rapid steroid taper from 200 mg to 20 mg over 5 days. The remaining 20 patients were given 20 mg of IV methylprednisolone immediately after transplantation and daily thereafter (20 mg of prednisone once the oral route was reestablished). During the subsequent months, the prednisone dose was slowly tapered. Twelve patients (50%) were completely weaned off steroids at 3 months to 1 year following transplantation. Eleven patients (45%) are still receiving low-dose prednisone (average of 10.9 ± 2.0 SE mg/d, range 5 to 20) in addition to FK 506.

Other Immunosuppressants. One patient, initially transplanted under FK 506, was switched to CyA 3 months after transplantation because of severe anorexia. He did not improve after the switch-over, but remained on CyA and parenteral nutrition. No patients received azathioprine.

Statistical Analysis
Actuarial survival was determined by the Kaplan-Meier method using BMDP-PC statistical software, Vernon PC-90 (BMDP, Los Angeles, Calif).

RESULTS
Patient and graft actuarial survival rates were 87.9% and 84.5%, respectively (Fig 1), at 6 months, and remained the same at 12 and 18 months. Two patients required retransplantation for primary nonfunction. No grafts were lost to rejection.

There were a total of three deaths, all of them in the

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Fig 1. Patient and graft actuarial survival defined by the Kaplan-Meier method.

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postoperative period. These were due to multiple cerebral infarcts, disseminated aspergillosis, and necrotizing pancreatitis. The remaining 24 patients are alive and well with a mean follow-up of 321 ± 35.1 SE days (range 30 to 572).

Rejection Episodes
Nine patients (33.3%) did not have a single episode of rejection. Another nine patients (33.3%) received a total of nine methylprednisolone boluses for suspected but not histological proven rejection. The remaining nine patients (33.3%) had a total of 11 episodes of acute rejection. Five episodes were managed with adjustment of the baseline immunosuppression, and five episodes with a bolus of methylprednisolone, in addition to adjusting the baseline immunosuppression. No steroid recycles were given, and on only one occasion was OKT3 required.

On average, patients received a total of 0.6 methylprednisolone 1-g boluses during the follow-up period.

Viral and Fungal Infections
In addition to the patient who died of disseminated aspergillosis, fungal infection was present in two other cases. One patient, with uncontrolled biliary sepsis secondary to primary sclerosing cholangitis, developed multiple intra-abdominal abscesses postoperatively which grew candida. He was successfully treated with amphotericin and open drainage of the abdomen. Another patient presented with cutaneous blastomycosis of the upper extremity 17 months after transplantation. He was treated with local excision.

Eight patients (29.6%) developed cytomegalovirus (CMV) infections following the transplant. Four patients (14.8%) developed asymptomatic CMV shedding, while the remaining 4 patients (14.8%) developed symptomatic disease and were successfully treated with gancyclovir.

Five patients presented with mucocutaneous herpes that responded to oral acyclovir. There were no Epstein-Barr virus infections.

Renal Function
Illustrated in Fig 2 are the serum creatinine means ± SE for all 27 patients at selected time points. Included are two patients who developed acute renal failure after transplantation, which required temporary hemodialysis. Note the rise in serum creatinine during the first week posttransplant followed by a progressive decline during the subsequent weeks. The mean serum creatines were 1.47 mg/dL ± 0.11 SE at 3 months, 1.5 mg/dL ± 0.08 SE at 6 months, and 1.36 mg/dL ± 0.08 SE at 12 months.

Diabetes, Neurotoxicity, and Other Side Effects
Two of the surviving 24 patients were insulin-dependent diabetics before and remained so after transplantation. Of the 22 patients who were nondiabetic, 4 (18%) developed posttransplant diabetes, although only 2 have required insulin therapy.

Fig 2. The mean serum creatinine ± standard error of the mean (SE) at selected time points in the 27 liver transplant recipients.

None of the patients suffered from serious neurotoxicity episodes such as seizures, unconsciousness, or expressive aphasia. Several patients had minor side effects such as photophobia, insomnia, headaches, etc., all of which subsided or significantly improved after appropriate dose adjustments of the FK 506.

DISCUSSION
In reviewing the literature, two institutions have reported results of liver transplantation under CyA in veterans. In one report, 16 veterans and 31 private patients were analyzed together. Although the 1-year actuarial survival was 80%, no reference was made to the outcome of the veterans as a group.

A second report analyzed 67 veterans who were transplanted and managed at our hospital (Presbyterian–University Hospital of Pittsburgh). Although the reasons for the outcome reported here were not clearly identified, their conclusion was that the results of liver transplantation (67% actuarial survival) obtained in veterans were not as good as those obtained in the civilian sector.

In this study, we present a group of 27 veterans transplanted under FK 506 immunosuppression. All were transplanted and managed at a veterans affairs facility. As shown in Table 1, this was not a particularly low-risk group of patients: 51% had a high UNOS score, 49% had previous upper abdominal surgery, and 22% required portal vein grafts. Therefore, an actuarial survival of 87.9% under FK 506 immunosuppression compares favorably to the 67% obtained under CyA.

Few patients required additional immunosuppression, such as OKT3 and/or steroid recycles, which may explain the low incidence of CMV and other opportunistic infections. The incidence of CMV infection reported here was only half of that reported under CyA, and similar to the incidence reported by Alessiani in the University of Pittsburgh FK 506 trials.

Although a potent immunosuppressant, FK 506 has shown an acceptable therapeutic index, at least in our experience, since: (1) no patient experienced serious neurotoxicity; (2) the 18% incidence of posttransplant diabetes...
is within the expected range for organ transplantation\(^7\)–\(^{11}\); and (3) the moderate degree of nephrotoxicity is similar to that reported by the University of Pittsburgh in the randomized trials, for both FK 506 and CyA.\(^{11}\)

REFERENCES