Initial studies with FK506 in renal transplantation

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■ FK506 is a novel immunosuppressive agent which is approximately 100 times as potent as cyclosporine in vitro. In this initial trial, 65 renal transplant patients of high complexity received primary FK506 immunosuppression. Overall, graft and patient survival rates are 80% and 98.5%, respectively. A major advantage of FK506 is its potency with relatively few side effects, which has permitted elimination of steroids in 31 (60%) of these patients. Because of these encouraging results, a randomized trial comparing the therapeutic efficacy and toxicity of FK506 and cyclosporine is currently underway at our institution.

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FK506 is a novel immunosuppressive agent derived from the fungus *Streptomyces tsukubaensis*.[1] The chemical structure of FK506, a neutral macrolide, is completely different from that of cyclosporine (CSA), a cyclic peptide. Furthermore, FK506 and CSA have different cytosolic binding sites.[2] Despite these differences, FK506 and CSA have similar immunosuppressive effects in vitro: both inhibit interleukins 2, 3, and 4 (IL-2, IL-3, IL-4), interferon gamma, and the production and generation of cytotoxic cells in mixed leukocyte culture (MLC). However, FK506 is approximately 100 times as potent as CSA in vitro.[3] Although both FK506 and CSA inhibit early activation events of T-cell maturation and IL-2 synthesis, the proliferative responses to IL-2 and IL-4 are relatively unaffected.[4]

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PHARMACOLOGIC ACTIVITY

The pharmacokinetics of FK506 and CSA differ.[5] FK506 is absorbed more rapidly than CSA, but both drugs require oral doses three to four times higher than intravenous doses to maintain similar plasma concentrations. Both FK506 and CSA are metabolized primarily by the liver, so that dosing of both drugs must be adjusted in the presence of impaired liver function or drugs that induce or inhibit hepatic enzymes. As with CSA, less than 2% of FK506 is excreted unchanged in the urine; therefore, changes in renal function are unlikely to affect the elimination of FK506. T-tube clamping experiments performed in dogs suggest that bile is not as essential for absorption of FK506 as for CSA.[5] In fact, experimentally induced cholestasis actually enhances the bioavailability of FK506. Therefore, in the presence of hepatic dysfunction, CSA doses must be increased, whereas FK506 doses must be decreased.

INITIAL STUDY CRITERIA

Encouraging results with FK506 in rescuing rejecting liver grafts maintained on CSA[6] and as primary

immunosuppression in liver transplants[7] led to an initial trial of FK506 therapy in renal transplantation.[8] This initial trial consisted of a complex group of 36 renal transplant recipients, of whom 10 had a prior liver transplant, 10 were undergoing retransplantation, and 2 were receiving a third organ (heart or pancreas) in addition to a liver and kidney. There were 34 cadaveric renal transplants and 2 living related transplants. Five cadaver donors were 57 to 64 years old, and en bloc pediatric kidneys (ages 4 to 26 months) were used in 8 cases.

No attempt at intentional human leukocyte antigen (HLA) matching was carried out in the cadaveric transplants. In fact, no patients had better than a three-antigen match, and over 50% had a one- or zero-antigen match. Twenty-five patients (75%) had four or more HLA mismatches.

In this series, FK506 was given every 12 hours as a continuous IV infusion of 0.075 mg/kg over 4 hours, until starting oral doses of 0.15 mg/kg bid when tolerated. Prednisone was started at 200 mg daily and tapered to a daily maintenance dose of 20 mg by day 6. Rejection episodes were treated by 1-g boluses of methylprednisolone followed by a 3- to 7-day course of OKT3 (muromonab-CD3) 5 to 10 mg/day, with additional steroids if necessary.

SHORT-TERM RESULTS

Primary function (early diuresis and freedom from dialysis for the first postoperative week) was present in both living related grafts and in 28 of 34 cadaveric grafts (82%). At follow-up of 4 to 13 months, 29 (81%) are dialysis-free. Of the 29 dialysis-free patients, 20 are receiving no or low-dose (2.5 to 5.0 mg/d) prednisone. Only one kidney was lost to cellular rejection; 3 of 9 patients who had antidonor cytotoxic antibodies in current or historical sera lost their grafts to irreversible humoral rejection.

Observed side effects of FK506 included nausea, vomiting, headaches, tremors, light sensitivity, insomnia, burning or tingling of the palms or soles, mood changes, tinnitus, and a sensation of "racing." Most of these symptoms were regarded by the patients as minor annoyances and have since been helpful in predicting a need for FK506 dosage reduction. Hirsutism and gingival hyperplasia, both of which are associated with CSA therapy, were not observed in this study population.

Additional follow-up

Since this original series of 36 patients of high complexity, we have reported a follow-up of the 26 kidney recipients from this series in addition to 39 more treated through June 1990.[9] Of these 65 patients, 2 received living related grafts; the rest received cadaveric grafts. There were 43 (65%) primary transplantations, and 23 patients were receiving their second to fourth grafts. Thirty patients were presensitized (panel reactive antibody [PRA] >10%); 20% of the patients had PRA >40%. Pediatric en bloc kidneys from donors under 3 years old were used in 16 cases (24%). The mean cold ischemia time of the cadaveric grafts was 36 hours. As in the first series, FK506 and prednisone were the sole agents used for primary immunosuppression. Rejection episodes were treated with additional steroids or OKT3 5 to 10 mg/day. The first 25 patients received a tapering prednisone dose (200 mg to 20 mg daily over 6 days); the next 40 patients were given only 20 mg of prednisone daily from the outset.

Currently 52 of the 65 patients (80%) are dialysis-free with a mean serum creatinine of 2.2 mg/dL. Initial function occurred in 41 patients (62%); 25 had acute tubular necrosis. There were a total of 14 graft losses. Causes of graft loss included irreversible rejection (n=8), patient death (n=1), thrombosed donor renal artery (n=1), and a mycotic pseudoaneurysm of the arterial anastomosis (n=1). Three grafts that continue to have good flow on nuclear scan but no rejection on biopsy are considered to have primary nonfunction and, hence, are regarded as graft losses.

Currently, among 52 patients out of the original 65 with functioning grafts, 31 (60%) are receiving no steroids, 8 (15%) are on 2.5 to 5 mg/d, and 12 (23%) are taking 10 to 20 mg/d. Forty-five patients (87%) are either on no or one antihypertensive drug. Serum cholesterol is 172 mg/dL (SD ±38), which is in the lower range of normal, and uric acid levels are 7.8 mg/dL (SD ±2.2), which is in the high range of normal. Five of the 52 patients developed de novo insulin-dependent diabetes following transplantation. The one death in this series was due to a myocardial infarction.

INFECTION

Infections occurred in 33% of the patients, and none were lethal.[10] Of 15 bacterial infections, 8 (53%) occurred in the urinary tract and were mild. Peritonitis following cecal perforation occurred in one patient with colonic pseudo-obstruction. There were two superficial wound infections and four patients had *Clostridium difficile* colitis. Viral infections occurred in 10 patients, and cytomegalovirus accounted for 8 of

these (7 had gastritis and 1 had viral syndrome). One patient had recurrent genital herpes, and one had reactivation of Epstein-Barr virus. The rates of infection were approximately half of those historically observed with CSA immunosuppression.[10]

CONCLUSION

The results of these initial studies with FK506 have been encouraging. The major side effects of FK506 are nephrotoxicity, neurotoxicity, and diabetogenicity,[8] but these appear to be much less severe than with CSA. Similarly, hypercholesterolemia, hyperuricemia, and hypertension, which have been prominent complications in CSA regimens, appear to be much less significant with FK506. Finally, the immunosuppressive potency of FK506 has permitted FK506 monotherapy in many patients; the reduction in the need for steroids may itself justify the use of FK506 over CSA. A randomized trial comparing FK506 and CSA is currently underway at the University of Pittsburgh. It is hoped that randomized trials such as this will shed more light on the comparative therapeutic efficacy and toxicities of FK506 and CSA.

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