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FK506 in Solid Organ Transplantation

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Summary: FK506 (Prograf) is a new immunosuppressive agent, recently approved for use in solid organ transplants. The first use of FK506 was for the indication of refractory liver allograft rejection. This revealed a marked ability to reverse ongoing rejection, even in cases where chronic changes were observed. Between 50 and 70% of patients converted to FK506 had shown improvement. In long-term follow-up of patients with chronic rejection, 75% of patients were still alive at 3 years following FK506 conversion, and 65% of liver allografts were still functioning. FK506 has been compared to cyclosporine in primary liver transplantation. In the three randomized trials, freedom from rejection was statistically greater in the FK506-treated group, as compared to the cyclosporine-treated group. By intent-to-treat analysis, the patient and graft survival in the FK506 group was the same or better than the cyclosporine group. The good results in the cyclosporine limb was due, in part, to the ability of FK506 to treat rejection in the cyclosporine group. Freedom from steroid use, and the lower incidence of hypertension, were prominent features of FK506 patients. FK506 has been used for rescue of rejecting kidney allografts, with results similar to the liver transplant trials. When used as primary immunosuppression, FK506 was shown to be effective, as measured by graft survival. FK506-based immunosuppression has also been used in primary heart transplantation, as well as for primary adult pulmonary transplantation. Results from these small series of patients are equally encouraging. The results of these studies suggest that FK506 is effective for solid organ transplantation. Both FK506 and cyclosporine administration have been associated with side effects, many of which are similar, and some of which are peculiar to a given organ transplant. **Key Words:** Tacrolimus—FK506—Solid organ transplantation.

FK506 (Prograf), a macrolide antibiotic produced by the fungus *Streptomyces tsukubaensis* is a new immunosuppressive agent (1–4). The first clinical use of FK506 was for the indication of uncontrolled liver allograft rejection, which was therefore considered treatment failure of conventional immunosuppression (5–11). The results of this experience revealed a marked ability to reverse ongoing rejection, even in cases where chronic changes were observed. Between 50 and 70% of patients treated by conversion to FK506 had both clinical and histopathologic improvement. In a recent long-term follow-up of 113 patients with chronic rejection, 75% of patients were still alive at 3 years following FK506 conversion, and 65% of liver allografts were still functioning (8).

Following an initial experience with FK506 as primary immunosuppression following liver transplantation at the University of Pittsburgh (12,13), FK506 has been compared to cyclosporine in primary liver transplantation, in randomized, nonblinded studies. At the University of Pittsburgh, low-risk candidates were randomized to FK506 with steroids as compared with cyclosporine with

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steroids (14,15). One hundred fifty-four patients were studied, and the 1-year patient and graft survival, as analyzed by intent to treat, was 92 and 88%, respectively, for FK506, compared with 85% and 79%, respectively, for cyclosporine. The follow-up at 2 years revealed that the modest increase in patient and graft survival in the FK506 limb was retained. The good results in the cyclosporine limb was due, in part, to the ability of FK506 to treat rejection in the cyclosporine group. The freedom from rejection was statistically greater in the FK506-treated group, as compared with the cyclosporine-treated group. In addition, the freedom from steroid use, and the lower incidence of hypertension, were prominent features of patients treated with FK506. The subsequent conversion of baseline immunosuppression from CsA-based regimens to FK506 at the University of Pittsburgh was associated with significant improvement in both patient and graft survival, when compared with immediately preceding eras of CsA based therapies (16).

The results of the University of Pittsburgh studies compare favorably to two other randomized liver transplant trials in both the United States and Europe (17,18). In each series, >500 patients were entered into the combined FK506 and CsA limbs. Both trials utilized a regimented FK506 treatment arm, although at higher initial FK506 dosages than have been utilized at the University of Pittsburgh. The European study demonstrated an enhanced patient and graft survival in the FK506 limb, when compared with the CsA limb, although this did not reach statistically significant difference. Although patient survival was similar in both groups in the American study, there was a slight benefit in graft survival in the FK506 limb. In both studies, there was less rejection in the FK506 limb, and the overall dose of steroids was less in the FK506 limb. By protocol design, crossover from CsA to FK506 was allowed for refractory rejection, while crossover from FK506 to CsA was allowed for adverse events in the FK506 limb only. With these conditions, the refractory rejection rates in the European study for FK506 was 2.9%, whereas that for the CsA limb was 10.4%. In the American study, the corresponding rates of refractory rejection was 3.0 and 14.8%, respectively. The differences in refractory rejection were significantly different, and the majority of CsA refractory rejections were rescued by conversion to FK506. The ability of FK506 to rescue CsA failures was the major reason that the survival in the CsA limb was retained at levels equivalent to the FK506 limb.

The application of FK506 rescue therapy to kidney transplantation was an extension of the experience gained in liver transplantation (19,20). The main difference between the two organ systems is the predominance of arteriopathy and sclerosis of epithelial structures in the kidney allografts undergoing chronic rejection. This was found to limit the ability of FK506 to rescue grafts with this pathologic finding. In a series of 35 patients, those with ongoing acute cellular rejection had a successful conversion rate of 71%, whereas those with stigmata of chronic rejection were not able to be rescued. Those with living related kidney transplants had a higher rate of rescue (73%) as compared with those with cadaver grafts (50%), probably related to an earlier referral for FK506 rescue therapy.

A randomized trial, utilizing FK506 in a double drug regimen (FK506 and steroids) versus a triple drug regimen (FK506, steroids, and azathioprine), was performed in kidney transplantation at the University of Pittsburgh (21). Two hundred four patients were enrolled; there were no specific exclusion criteria based on immunologic or transplant history. The 1-year actuarial patient and graft survival for the two-drug versus three-drug regimen were 95 and 90% versus 91 and 82%, respectively. No differences were noted in kidney function with mean serum creatinine of 1.8 ± 0.8 mg/dl. The rejection rate in the three-drug regimen was less than that for the two-drug regimen (10% vs. 51%), although this was not statistically significant (p = 0.07). Crossover from one group to another was not uncommon, 25% of the two-drug group were given azathioprine, principally because of rejection, whereas 45% of the three-drug group required discontinuation of azathioprine because of leucopenia or hepatic dysfunction.

FK506-based immunosuppression has also been used in heart transplantation at the University of Pittsburgh (22). Seventy-two adult patients were given FK506 as primary immunosuppression following heart transplantation. The 1-year patient and graft survival was 92%. The freedom from rejection at 90 days was 41% and at 180 days was 34%. Renal dysfunction was frequently noted, and the mean serum creatinine at 6 months following transplantation was 2.2 mg/dl. The incidence of diastolic hypertension was 54%, but was considered mild, as treatment consisted of a single agent in all cases. The incidence of new onset diabetes was 20% in this group of patients.

A prospective randomized trial of primary adult

pulmonary transplantation was conducted at the University of Pittsburgh (23). Azathioprine was combined with either FK506 or cyclosporine, with use of steroids only if the recipient encountered more than one episode of rejection. Twenty-eight patients were randomized to FK506 and 29 patients were randomized to cyclosporine. The 6-month graft survival was statistically better in the FK506 group as compared with the cyclosporine group (86 vs. 69% respectively; $p < 0.05$). Twenty-one percent of the FK506 patients were rejection free at 6 months, as compared with only 3% of the cyclosporine patients.

One way to assess the impact of a new immunosuppressive agent in transplantation is the ability to successfully transplant organs that was not considered feasible with standard immunosuppression. Success with intestinal transplantation under cyclosporine immunosuppression has been sporadic (24–26). A growing experience of small bowel transplantation, either alone, or combined with other abdominal organs, has been accumulated under FK506 at the University of Pittsburgh (27–30). Small bowel allografts have been transplanted alone ($n = 9$), together with liver ($n = 16$), or as part of a multivisceral cluster ($n = 3$). In these 28 patients, 82% were alive at a median follow-up of 9 months. Graft survival was 76% for the same period of time. Graft function was satisfactory, with 84% of survivors being totally enterally sufficient and the other 16% relying on supplemental parenteral nutrition. Rejection was not uncommon, with 90% of the patients having at least one rejection episode of the intestinal allograft. Rejection has been treated by additional steroids and addition of azathioprine; however, antilymphocyte preparations have been used occasionally.

The results of these studies suggest that FK506 is effective for solid organ transplantation. Nevertheless, FK506 is not without its limitations. Toxicity profiles for FK506 are similar to that for cyclosporine, perhaps because of similar mechanisms of action (31). Both FK506 and cyclosporine administration have been associated with side effects, many of which are similar, and some of which are peculiar to a given organ transplant (32,33). Adverse reactions requiring treatment or adjustment of FK506 doses can be categorized into four primary areas. These are (a) alterations in kidney function, (b) alterations in glucose metabolism, (c) neurotoxicity, and (d) susceptibility to infection or malignancy.

One of the major benefits of FK506 appears to be a relative lack of some of the side effects of cyclosporine. Some of these are cosmetic, such as hirsutism and gingival hyperplasia, which has not been seen with FK506. Other more significant side effects, such as hypertension, appear to be less in the FK506 patients than in those on cyclosporine. The ability to use less steroids in patients with FK506, when compared with cyclosporine, may result in less complications ascribed to chronic steroid use. In one study where FK506 was compared with cyclosporine in pediatric renal transplant recipients, 78% of all FK506 recipients were off steroids. Significant improvement in the growth pattern of preadolescents on FK506 monotherapy was noted when compared with those on FK506 and steroids or cyclosporine and steroids.

The primary side effects of FK506, are insomnia, tremors, headaches, tingling sensations, muscle achiness, itching, fatigue, visual sensitivity to light, and GI symptoms. Although it has taken >10 years to elucidate the limitations of cyclosporine therapy, we believe that the profile of adverse effects of FK506 has been determined. Schemes to minimize these effects should increase the safety of this agent for immunosuppression.

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