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# Tacrolimus in Renal Transplantation

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TACROLIMUS (Prograf-FK506) has been used since 1989 as a primary immunosuppressive agent in adult and pediatric renal transplant recipients at our institution.[1,2] This report will summarize our experience with it over the past six years and will demonstrate its overall efficacy and superiority.

## Adults

The early studies with tacrolimus, from 1989 through 1991, included a pilot series, a small randomized trial, and a larger nonrandomized group.[1,3,4] When the outcome of these patients was compared with that in a roughly concurrent (although somewhat less challenging) group of cyclosporine (CyA)-treated patients, equivalent patient and graft survival rates were seen. However, improved secondary outcomes were noted in the tacrolimus-treated patients, including lower steroid and antihypertensive medication requirements, and lower serum cholesterol levels.[4] This led to a second prospective, randomized trial, between August, 1991 and December, 1993, comparing two tacrolimus-based regimens, with and without azathioprine.[5–8] Earlier analyses of this trial (by intention to treat, without patient censoring) demonstrated excellent outcomes with tacrolimus overall, but with unclear benefit for azathioprine. The most recent analysis, with a mean follow-up of 33 ± 10 months, showed a one- and three-year actuarial patient survival of 95% and 92%, with no significant difference between the two groups (Table 1). Overall one- and three-year actuarial graft survival was 89% and 80%, with worse results in the tacrolimus/azathioprine/prednisone group than in the tacrolimus/prednisone group. Overall one- and three-year actuarial graft survival in first cadaver recipients was 91% and 82%, without a statistically significant difference between the two groups. The projected half-life of first cadaver kidneys was 11.9 ± 2.5 years.

**Table 1. Tacrolimus in Renal Transplantation Adults n = 397**

| | Tacro/Pred | Tacro/Aza/Pred | Overall |
|---|---|---|---|
| Actuarial Patient Survival | | | |
| 1 year | 97% | 94% | 95% |
| 3 year | 94% | 90% | 92% |
| Actuarial Graft Survival | | | |
| 1 year | 90% | 88% | 89% |
| 3 year* | 84% | 76% | 80% |
| *$P$ = .031 | | | |
| S. Creatinine (mg/dL) | 1.9 ± 1.0 | 1.9 ± 1.8 | 1.9 ± 1.5 |
| Off Steroids | 70% | 68% | 69% |
| Off Anti-Hypertensive Medications | 39% | 36% | 38% |

Sixty-nine percent of successfully transplanted patients have been taken off steroids, and 38% are off antihypertensive medications. The mean serum creatinine is 1.9 ± 1.5 mg/dL. There are no differences between the double and triple drug groups in these parameters. The incidence of rejection was 50%, and steroid-resistant rejection was seen in 11% of cases. There was a slightly lower, but not statistically different, incidence of rejection in the azathioprine group (45% vs 55% overall, and 8% vs 14% steroid resistance). There was also a substantial crossover between the two groups, more from triple to double therapy than vice versa.

Subsequent to completion of the second randomized trial, a third randomized trial was begun in December, 1993, evaluating the role of one week of low-dose cyclophosphamide in tacrolimus-treated recipients. Analysis of this trial is currently in progress, and a fourth randomized trial, comparing tacrolimus/prednisone and tacrolimus/prednisone/mycophenolate mofetil, has just begun.

## Pediatrics

Between December, 1989 and December, 1993, 43 pediatric patients received kidneys under tacrolimus-based immunosuppression (concomitant or previous liver recipients were excluded from this analysis).[2] With a mean follow-up of 25 ± 14 months, overall one- and three-year actuarial patient survival was 100% (Table 2). Overall one- and three-year actuarial graft survival was 98% and 85%. Sixty-two percent of the successfully transplanted children have

**Table 2. Tacrolimus in Renal Transplantation Pediatrics n = 43**

| Actuarial Survival | | |
|---|---|---|
| | 1 year | 3 year |
| | 100% | 100% |
| Patient Graft | 98% | 85% |
| S. Creatinine | 1.2 ± 0.6 mg/dL | |
| Off Steroids | 62% | |
| Off Anti-Hypertensive Medications | 62% | |

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been weaned off steroids, and 62% are not taking antihypertensive medications. The mean serum creatinine is 1.2 ± 0.6 mg/dL. The incidence of rejection was 58%, and the incidence of steroid resistant rejection was 7%. An additional 26 children were transplanted between January, 1994 and July, 1995, with 100% patient and graft survival.

The overall experience with tacrolimus in our renal transplant patients has been gratifying. Better short-term graft survival, longer projected half-lives, and a remarkable ability to wean from steroids in a majority of patients have been the most notable observations. Based on these findings, we believe that tacrolimus is a superior immunosuppressive agent in renal transplant recipients and is, at present, the drug of choice. The prolongation of cadaver kidney half-life in patients treated with tacrolimus is similar to that reported by Gjertson, Cecka, and Terasaki in a collection of cases compiled in the United Network for Organ Sharing (UNOS) Scientific Registry from 24 American renal transplant centers.[9] Ongoing work is continuing to evaluate the role of new third agents and other modalities (eg bone marrow augmentation)[10,11] in an effort to improve further the outcomes after transplantation.

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