



Outcome After Steroid Withdrawal in Adult Renal Transplant Patients Receiving Tacrolimus-Based Immunosuppression

P. Chakrabarti, H.Y. Wong, A. Toyofuku, V.P. Scantlebury, M.L. Jordan, C. Vivas, A.B. Jain, J. McCauley, J. Johnston, P.S. Randhawa, T.R. Hakala, R.L. Simmons, J.J. Fung, T.E. Starzl, and R. Shapiro

CORTICOSTEROIDS, in spite of their well-known side effects, have essentially always been an integral part of immunosuppressive regimens in renal transplantation. With the introduction of tacrolimus, however, steroid withdrawal has been possible in some 70% of successfully transplanted adults and children.¹⁻⁸ An important question, however, concerns the outcome after steroid withdrawal in adult patients on tacrolimus. We looked at our adult renal transplant patients receiving tacrolimus-based immunosuppression and examined the short- and medium-term outcomes after steroid withdrawal.

PATIENT AND METHODS

Between August 1991 and December 1996, 795 renal transplants were performed in adult patients receiving tacrolimus-based immunosuppression at the University of Pittsburgh. 43 (5%) of these grafts were lost within 3 weeks of transplantation, and the recipients were still on steroids at the time of graft loss, and 4 were lost to follow-up; both groups were excluded from further analysis. The mean recipient age was 46 ± 14 years (range 18-84). Five hundred fifty-four (74%) were primary transplants, and 194 (26%) were second ($n = 144$), third ($n = 39$), or fourth ($n = 11$) transplants. Four hundred forty-two (59%) were males and 306 (41%) were females. Six hundred three (81%) were whites, 116 (15%) were African-Americans, and 29 (4%) were Asians. The mean PRA was $11 \pm 22.5\%$ (range 0 to 100).

The mean donor age was 36 ± 19 years (range 0.1 to 77). Six hundred fifty-six (88%) kidneys were from cadaveric donors. The mean cold ischemia time was 30.7 ± 9.5 hours. There were 92 (12%) living donors. The mean number of HLA matches and mismatches was 2.7 ± 1.4 and 2.9 ± 1.5 , respectively. The mean number of DR-matches and mismatches was 1.1 ± 0.6 and 0.8 ± 0.7 , respectively.

Immunosuppression was with tacrolimus and steroids with or without azathioprine, mycophenolate mofetil, or a one week course of low-dose cyclophosphamide, as previously described.¹⁻³ Induction antilymphocyte antibodies were generally not used. Although there were no formal a priori inclusion or exclusion criteria for complete withdrawal, steroids were tapered and discontinued in patients who maintained stable allograft function as the steroid dosage was gradually decreased. Steroids were restarted in recipients who experienced a rising serum creatinine with biopsy-proven acute rejection. Allograft failure was defined by return to dialysis, retransplantation, or death.

Patient survival was calculated from the date of kidney trans-

plantation until death, and graft survival was calculated from the date of kidney transplantation until graft failure or patient death. Survival curves were generated using the Kaplan-Meier (Product limit) method and were compared using the log-rank test. Values are presented as mean \pm SD. A time dependent Cox regression analysis for hazard assumption was done to compare graft survival in recipients who came off steroids versus those who never came off. A Cox time dependent covariate $z(t)$ was modeled, so that $z(t) = 1$ if the patient was weaned off at least once, and $z(t) = 0$ if the patient was not weaned off by time t .

A multivariate multiple logistic regression analysis was performed to compare the effect of recipient sex, recipient race, delayed graft function, recipient PRA, total HLA-matches, total-HLA mismatches, donor age, and donor type (cadaveric vs living related) on steroid withdrawal. The means between groups were compared by one way analysis of variance (ANOVA). Categorical data were analyzed by Pearson chi-square method. P values less than 0.05 were considered statistically significant.

RESULTS

Five hundred thirty-one (71%) patients were taken off prednisone a median of 9.7 months after transplantation. Of these 531 patients, 398 (75%) remained off prednisone (OFF), and 133 (25%) were restarted on prednisone a median of 14.5 months after discontinuing steroids (OFF/ON). Two hundred seventeen (29%) were never taken off prednisone (ON). The mean follow-up was 4.6 ± 2.6 years. The 1, 3, and 5 year actuarial patient survival rates in the OFF group were 99.7%, 98%, and 96%, respectively; in the OFF/ON group, they were 99%, 98%, and 93%. ($P = NS$ compared to the OFF group), and in the ON group, they were 91%, 82%, and 78% ($P = .0001$ compared to the OFF and OFF/ON groups). The 1, 3, and 5 year actuarial graft survival rates in the OFF group were 99.5%, 96%, and 89% respectively; in the OFF/ON group, they were 98.5%, 89%, and 71%, and in the ON group, they were 74%, 52%, and

From the Thomas E. Starzl Transplantation Institute, Division of Urologic Surgery, Division of Nephrology, Department of Pathology, and Division of General and Vascular Surgery, University of Pittsburgh, Pittsburgh, PA 15213, USA

Address reprint requests to Dr Ron Shapiro, 3601 5th Ave, 4th Floor, Pittsburgh, PA 15213.

42% ($P = .0001$). A Cox regression analysis showed that the hazard assumption for graft failure for those who came off prednisone was 0.124 relative to those who were never off prednisone ($P < .0001$). Acute rejection-free survival was 65% in the OFF group compared to 20%, and 24% in the OFF/ON and ON groups respectively ($P < .05$). The incidences of steroid resistant rejection episodes were 4% in the OFF group, and 12%, and 22% in the OFF/ON, and ON groups respectively ($P < .001$). There were 82 (21%) retransplants in the OFF group, 33 (25%) in the OFF/ON group, and 66 (30%) in the ON group ($P < .001$). The mean PRA was higher in the ON group $14.9 \pm 26\%$, than in the OFF group, $9.4 \pm 20.6\%$, and the OFF/ON group, $10.2 \pm 20.4\%$ ($P = .01$). There was no effect of donor race and sex, recipient race and sex, cadaveric vs living donor, 48-hour graft function, and total HLA mismatches or matches on the likelihood of being weaned off steroids. In the OFF group, the serum creatinine at most recent follow-up was 1.8 ± 1.7 mg/dL; in the OFF/ON and ON groups, it was 3.7 ± 2.9 mg/dL and 4.5 ± 3.8 mg/dL, respectively ($P = .0001$). In the OFF group, the hematocrit at most recent follow-up was 40 ± 7.2 ; whereas, in the OFF/ON and ON groups, it was 35 ± 7.3 , and 33 ± 7.9 respectively ($P = .01$). The mean tacrolimus level in the OFF group was 8.2 ± 3.9 ng/mL at last follow-up; in the OFF/ON and ON groups it was 8.3 ± 4.1 ng/mL, and 10.5 ± 6.6 ng/mL, respectively ($P = .03$).

DISCUSSION

The primary goal of this analysis was to assess the safety of steroid withdrawal in our adult renal transplant recipients receiving tacrolimus-based immunosuppression. The main questions for us concerned the safety of steroid withdrawal and, more importantly, the outcomes in patients who were withdrawn from and then resumed steroids. It should be

emphasized that patients were not randomly assigned to steroid withdrawal, and patients who never came off (ON), and those who were withdrawn from and then resumed steroids (OFF/ON), had a number of risk factors, including retransplantation, sensitization, and acute rejection. Five year patient survival rates were essentially the same in the OFF and the OFF/ON groups, but 5-year graft survival rates were significantly lower in the OFF/ON group compared to the OFF group. The incidence of rejection and the mean serum creatinine were higher in the OFF/ON group, and these findings are of concern with regard to long term follow-up.

To summarize, these data suggest that steroid withdrawal in adult renal transplant patients receiving tacrolimus-based immunosuppression is associated with reasonable medium-term patient and graft survival and reasonable graft function. The patients who discontinued and then resumed steroids had comparable patient survival, but lower graft survival and worse renal function. The patients who never discontinued prednisone had the worst outcome.

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