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A Prospective, Randomized Trial of Tacrolimus/Prednisone vs Tacrolimus/Prednisone/Mycophenolate Mofetil in Renal Transplantation: 1-Year Actuarial Follow-Up

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BETWEEN September 10, 1995, and September 20, 1997, a total of 208 adult patients undergoing their first or second cadaveric renal transplantation alone were randomized to receive tacrolimus/prednisone ($n = 106$) or tacrolimus/prednisone/mycophenolate mofetil ($n = 102$), without induction antilymphocyte antibody therapy. The mean recipient age was 50.8 ± 13.7 years (range 19 to 84). Thirty-one (14.9%) patients were undergoing their second transplant, and 11 (5.3%) had a panel-reactive antibody level of over 40%. Sixty-three (30.3%) patients were 60 years of age or older at the time of transplantation, and 16 (7.7%) patients had undergone previous liver or heart transplantation. The mean donor age was 34.5 ± 21.7 years (range 0.01 to 76.5). Twenty-eight (13.5%) donors were 60 years of age or older, and 25 (12.0%) donors were 3 years of age or younger, and were transplanted en bloc. The mean cold ischemia time was 30.5 ± 9.2 hours (range 4.7 to 57.1). The mean number of HLA matches and mismatches was 2.5 ± 1.4 and 3.1 ± 1.5 , respectively. There were 17 (8.2%) 0 antigen mismatches. The mean follow-up was 15 ± 17 months.

The data were analyzed by intention-to-treat. The overall 1-year actuarial patient survival was 94%; in the double therapy group, it was 93%, and in the triple therapy group, it was 96%. Overall 1-year actuarial graft survival was 87%; in the double therapy group, it was 85%, and in the triple therapy group, it was 89%. When the patient and graft survival data were stratified to recipients under the age of 60 who did not have delayed graft function, the overall 1-year actuarial patient survival was 97%, 95% in the double therapy group, and 98% in the triple therapy group. The corresponding 1-year actuarial graft survival was 93%, 92% in the double therapy group, and 93% in the triple therapy group.

The mean serum creatinine was 1.6 ± 0.8 mg/dL, 1.6 ± 0.9 mg/dL in the double therapy group and 1.7 ± 0.7 mg/dL in the triple therapy group. The mean tacrolimus dose was 8.7 ± 6.6 mg/d; in the double therapy group it was 8.4 ± 6.0 mg/d, and in the triple therapy group, it was 9.0 ± 7.1 mg/d. The mean tacrolimus level was 10.1 ± 4.4 ng/mL; in the double therapy group, it was 10.2 ± 4.5 ng/mL, while in the triple therapy group, it was 10.1 ± 4.2 ng/mL. The mean MMF dose in the patients taking MMF was 1142 ± 493 mg/d.

Thirty-six percent of the successfully transplanted patients were taken off prednisone, 34% in the double therapy

group and 39% in the triple therapy group; 32% of the patients were taken off antihypertensive medications, 25% in the double therapy group and 39% in the triple therapy group. Then mean serum cholesterol level was 196 ± 55 mg/dL, and was 200 ± 62 mg/dL in the double therapy group, and 192 ± 46 mg/dL in the triple therapy group.

Overall incidence of rejection was 36%; in the double therapy group, it was 44%, while in the triple therapy group, it was 27% ($P < .012$). In the triple therapy patients who never came off MMF, the incidence of rejection was 16%, while in those discontinuing MMF, it was 49%. In addition, there was a trend toward more severe rejections in the double therapy group. The overall incidence of steroid-resistant rejection was 5.3%; in the double therapy group, it was 7.5%, whereas in the triple therapy group, it was 2.9%. The incidence of delayed graft function was 21%, 21% in the double therapy group, and 21% in the triple therapy group. Incidence of cytomegalovirus was 12.5%, 8.5% in the double therapy group and 16.7% in the triple therapy group ($P = NS$). The initial and final incidences of posttransplant diabetes mellitus were, respectively, 7.0% and 2.9%, 9.3% and 4.7% in the double therapy group, and 4.7% and 1.2% in the triple therapy group. The overall incidence of crossover was 31%, 28% from double to triple therapy, and 34% from triple therapy to double therapy; in the second year of the trial, the incidence of crossover from triple to double therapy decreased to 12%.

These data suggest that the combination of tacrolimus, mycophenolate, and prednisone is associated with a lower incidence of rejection than the combination of tacrolimus and steroids, although there is no difference in patient or graft survival at 1 year. There are side effects associated with triple therapy, but they have been generally manageable with dosage reduction. Finally, this trial suggests that the combination of tacrolimus and MMF is associated with excellent patient and graft survival, and a low incidence of rejection.

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