



2181

A Pilot Trial of Tacrolimus, Sirolimus, and Steroids in Renal Transplant Recipients

R. Shapiro, V.P. Scantlebury, M.L. Jordan, C.A. Vivas, A. Jain, T.R. Hakala, J. McCauley, J. Johnston, P. Randhawa, S. Fedorek, E. Gray, A. Chesky, I. Dvorchik, J. Donaldson, J.J. Fung, and T.E. Starzl

IN RENAL transplant recipients, sirolimus has been studied extensively in combination with cyclosporine,¹ but relatively few published studies have looked at the combination of sirolimus and tacrolimus.²⁻⁵ We performed a pilot trial of tacrolimus, sirolimus, and steroids, without antibody induction and with protocol biopsies, to look at the safety and efficacy of this combination. This report describes the early outcomes in the first 30 patients entered into the trial.

PATIENTS AND METHODS

Thirty adults undergoing their first kidney transplantation alone, either with a cadaver ($n = 20$) or a living donor ($n = 10$) kidney, were entered into the trial. The mean recipient age was 50.7 ± 12.5 years (range 25.5 to 73.6). Patients undergoing previous extrarenal transplantation were excluded.

Immunosuppression consisted of tacrolimus (0.05 mg/kg PO) preoperatively, and (0.05 mg/kg PO BID) postoperatively. Target levels were 8 to 10 ng/mL for the first 3 months and 5 to 7 ng/mL thereafter. The first five patients entered into the trial received sirolimus (6 mg PO) preoperatively and (2 mg ($n = 4$) or 5 mg ($n = 1$) PO qd) postoperatively. The remaining 25 patients received sirolimus (15 mg PO) preoperatively and (5 mg po qd) postoperatively (one patient developed immediate thrombocytopenia and did not receive any sirolimus postoperatively). Target sirolimus levels were 6 to 10 ng/mL for the first 3 months and 5 to 7 ng/mL thereafter. All patients received 1000 mg IV methylprednisolone intraoperatively and a 6-day recycle from 200 \rightarrow 20 mg/day of either intravenous methylprednisolone or oral prednisone. Further steroid tapering was individualized but generally followed our previously described protocols.⁶ Antibody induction was not used.

The mean cold ischemia time for the 20 cadaver cases was 26.2 ± 6.1 hours. The mean number of HLA matches and mismatches was 2.5 ± 1.1 and 2.8 ± 1.2 , respectively.

Protocol biopsies were performed at approximately 1 week, 1 month, and 1 year after transplantation.

This pilot trial was approved by the Institutional Review Board of the University of Pittsburgh, and patients signed informed consent to participate.

RESULTS

The mean follow up was 7.7 ± 3.8 months. Patient survival was 97%; one patient died 5.7 months after transplantation of uterine carcinoma that was unknowingly present at the time of transplantation. Graft survival was 93%; one other

kidney was lost to thrombosis immediately after transplantation because of a hypercoagulable state in the recipient. The mean serum creatinine at most recent follow-up was 1.8 ± 0.7 mg/dL. The mean serum cholesterol was 192 ± 47 mg/dL; the mean serum triglyceride level was 245 ± 142 mg/dL. The mean platelet count was $218,000 \pm 56,000$.

In the five patients receiving 6 mg of sirolimus preoperatively, four had undetectable levels, and three had clinical ($n = 2$) or subclinical ($n = 1$) evidence of Banff 1A or worse rejection. In the 25 patients receiving 15 mg of sirolimus preoperatively, the incidence of clinical Banff 1A or worse rejection was 16%; the incidence of subclinical Banff 1A or worst tubulitis was 12%. The incidence of borderline changes, either clinical or subclinical, was 24%. The incidence of steroid-resistant rejection was 4%.

The mean tacrolimus levels were 10.2 ± 5.7 mg/mL at 1 week and 14.9 ± 5.7 mg/mL at 1 month. The mean sirolimus levels in the 25 patients receiving 15 mg preoperatively were 4.7 ± 1.7 ng/mL at 1 week and 7.4 ± 4.2 ng/mL at 1 month. Nine (30%) patients discontinued sirolimus; four because of thrombocytopenia and five for other reasons. The initial and final incidences of posttransplant diabetes mellitus (PTDM) were 24% and 10%. The incidence of delayed graft function was 24%. One sulfa-allergic patient developed *pneumocystis carinii* pneumonia on dapsone prophylaxis. Although she required transfer to the intensive care unit, intubation, and assisted ventilation, she eventually made a complete recovery and kept her allograft.

DISCUSSION

This nonrandomized pilot trial represented both an attempt to study the safety and efficacy of the combination of low-dose tacrolimus and sirolimus and an opportunity to obtain some experience using the combination of the two agents prior to performing a randomized trial. The combination seemed reasonably safe and efficacious. Among the lessons we learned was that the low initial dosages of

From the Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, Pennsylvania.

Address reprint requests to Dr R. Shapiro, Thomas E. Starzl Transplantation Institute, University of Pittsburgh, Pittsburgh, Pennsylvania.

sirolimus were associated with undetectable levels and a high incidence of rejection, and the sirolimus dosage had to be switched very early to 15 mg preoperatively and 5 mg postoperatively to obtain detectable levels. The subsequent incidence of clinical rejection of 16%, and the incidence of steroid-resistant rejection of 4% seemed reasonable; however, the additional 12% incidence of subclinical acute rejection was worrisome. In the future, a short course of antibody induction might be preferable to allow for protection until adequate sirolimus levels are achieved. Implicit in this reasoning is the absolute need to have ready access to sirolimus levels if one is to use the agent in a rational manner.

The opposing effects of tacrolimus and sirolimus on cholesterol were associated with reasonable cholesterol levels in our patients, although triglyceride levels tended to remain a bit elevated. Significant thrombocytopenia was relatively infrequent but did lead to sirolimus discontinuation in 13% of the patients.

In summary, the combination of tacrolimus, sirolimus, and steroids, without antibody induction, seemed to offer reasonable initial immunosuppressive safety and efficacy in renal transplant recipients. However, the lower initial dosages of sirolimus were associated with undetectable levels and a high incidence of rejection. If one is to use tacrolimus and sirolimus in combination, high initial sirolimus dosages are necessary to achieve detectable levels.

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