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New Onset of Diabetes in FK 506 Vs Cyclosporine-Treated Kidney Transplant Recipients

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THE development of diabetes mellitus in the renal transplant population was first reported by Starzl in 1964 and was attributed to the use of steroids.[1] Since then, posttransplant diabetes mellitus has been associated with the use of other immunosuppressive agents, such as cyclosporine (CyA). Because FK 506 is also thought to be diabetogenic,[2] we retrospectively looked at the incidence of new onset diabetes mellitus in patients treated primarily with either FK 506 or CyA in a randomized trial of kidney transplantations done at the University of Pittsburgh from February 1990 to May 1991.

MATERIAL AND METHODS

Patient Population

The criteria for randomization include (1) primary transplants, (2) patients between age 16 and 60 years, (3) PRA <40%, and (4) no hepatic or cardiac dysfunction. Fifty-five patients were entered into the study from February 20, 1990 to May 1, 1991. Twelve patients who were known diabetics prior to transplantation were excluded from analysis. Nine patients randomized to CyA and prednisone were switched to FK 506 and prednisone due to resistant rejection. These patients were therefore not included in the analysis. The final evaluation was then conducted on a group of 34 patients: 20 were treated with FK 506 and prednisone and 14 received CyA and prednisone.

Diabetes mellitus was defined as a fasting blood sugar greater than 150 mg/dL obtained on three separate occasions. Abnormal plasma glucose levels occurring while a steroid taper was being administered were not considered as a manifestation of diabetes if glucose levels returned to normal at the end of the steroid taper.

Immunosuppression

Prior to August of 1990, FK 506 was given in two daily doses of 0.075 mg/kg/dose over a 4-hour infusion. Patients received 20 mg of IV methylprednisolone in the recovery room and 20 mg of oral prednisone or IV methylprednisolone daily thereafter. CyA was given at 2 mg/kg/dose twice a day as a 2-hour infusion. After August 1990, FK 506 was changed to a continuous IV infusion over 24 hours of 0.1 mg/kg/d with a 6-day steroid recycle following an intraoperative bolus of 1,000 mg of IV methylprednisolone. The CyA dosage remained the same.

Rejection Episodes

Rejection as diagnosed by biopsy was treated with 1,000 mL of IV methylprednisolone with or without a 6-day steroid taper.

Analysis

Statistical analysis was calculated by Fisher Exact Test. Differences of $P < .05$ were considered significant.

RESULTS

Of the 24 patients analyzed, 4 out of 20 patients receiving FK 506 primarily became diabetic (20%) within 1 month after kidney transplantation. All four patients required insulin therapy for management of their hyperglycemia. FK 506 dosages were also decreased and steroids were tapered to zero when tolerated. One patient had concomitant rejection at the time of diagnosis of diabetes mellitus and had to be treated with extra steroids; all three remaining patients had their steroid therapy discontinued by 1 week in two of the patients, and by 4 weeks in the third case. Insulin therapy was discontinued at 4 and 6 weeks in two cases (50%) with one patient switching to a low dose oral hyperglycemic agent. The remaining two cases are still on insulin therapy at 12 months and 14 months following initiation of treatment.

Within the CyA group, the onset of new diabetes was seen in 1 out of 14 patients (7%). This patient developed diabetes within 2 weeks of transplantation but required only an oral hyperglycemic agent.

In analyzing both groups of patients, we find that age may play a role in the onset and persistence of diabetes mellitus. Two patients ages less than 40 years had resolution of diabetes; those older than 40 years had persistence of insulin-dependent diabetes beyond 1 year follow-up (two patients). One long-term diabetic patient who is off steroid therapy was found to have a HLA DR_4 typing; no other markers were found among the remaining patients.

Within the group of patients originally on CyA but switched to FK 506 (nine patients) there was one case of new onset diabetes mellitus. Since this patient was intensively treated for persistent rejection and received both main immunosuppressive drugs, he was not included in the final analysis.

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Supported by research grants from the Veterans Administration and Project Grant No. DK 29961 from the National Institutes of Health, Bethesda, MD.

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0041-1345/91/$3.00/+0

DISCUSSION

The occurrence of diabetes mellitus after kidney transplantation has been described in the literature as between 4% and 15%.[3–5] The incidence of diabetes mellitus with CyA is known to be higher than when compared with those receiving azathioprine and steroids. Since the first clinical trials of FK 506 it has been found that this drug alters carbohydrate metabolism by inhibiting insulin secretion and increasing peripheral insulin resistance. These characteristics are also true for CyA. The ability to use FK 506 with very low doses or no doses of steroids may lead to reduction in the incidence of posttransplant diabetes mellitus.

Our findings of a 20% incidence of new onset diabetes mellitus with FK 506 when compared with 7% incidence with CyA is not statistically significant. Since half of this new onset insulin dependence was reversible, the true incidence was 10%, similar to what has been seen with CyA.[3–5] It is important to realize, however, that diabetogenesis remains a significant side effect of FK 506.

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