

FK 506-Associated Diabetes Mellitus in the Pediatric Transplant Population is a Rare Complication

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FK 506 is a powerful new investigational immunosuppressant that has been used successfully first as an organ rescue agent and then as a primary antirejection agent. FK 506 has been shown to have a favorable profile on pancreatic islets in vitro¹; however, the agent does decrease glucose-induced insulin release at high concentrations from both rodent^{2,3} and human islets.² This agent also prolongs the clearance of glucose and decreases insulin release from transplanted dog islets in vivo,⁴ and is diabetogenic in some species of animals⁵ and more importantly in adult humans.⁶ The aim of this study was to evaluate the magnitude of the diabetogenic effect of FK 506 in pediatric patients undergoing organ transplantation.

METHODS

Patients who developed insulin-requiring diabetes were identified using a variety of methods including outpatient chart reviews, review of endocrine consults for diabetes management, information from transplant physicians and nurse coordinators, and contact with referring physicians to identify problems that occurred after hospital discharge.

RESULTS

From September 1989 to May 1991 206 children received FK 506 for the following indications: 108 primary liver transplants, 44 liver "rescues," 1 liver/kidney transplant, 3 liver/small bowel transplants, 22 primary kidneys, 9 kidney "rescues," 16 primary hearts, and 3 heart "rescues." Patients who had diabetes mellitus prior to the transplant and patients who underwent upper abdominal exenteration including pancreatectomy and pancreatic islet transplantation were excluded from the analysis. Only three pediatric patients developed insulin-requiring diabetes while on FK 506 as a single agent. All patients had been off steroids at least 1 week at the time that diabetes developed.

The three patients who developed diabetes were adolescents with liver disease who were switched to FK 506 in an attempt to rescue a previously transplanted liver with chronic rejection despite maximal standard immunosuppressive drugs. All patients were treated with cyclosporine (CyA) and steroids prior to the switch. CyA was stopped and FK 506 treatment was immediately instituted. Rejection was successfully managed in all patients initially; however, one patient required retransplantation for recurrence of autoimmune hepatitis 17 months after the switch (Table 1). Only one patient had a high plasma FK level at any time prior to developing diabetes (15 ng/mL, patient 3, Table 1). All patients have returned to full activities. Diabetes in the setting of organ rescue developed late (from 17 to 27 days). All patients were symptomatic from hyperglycemia and plasma glucose levels ranged from 326 mg/dL to >1,000 mg/dL. No patient had ketonuria. Only one patient was obese and this patient had evidence of mild acanthosis nigricans (a skin manifestation of insulin resistance) on the neck (patient 3). Two of the three patients had a positive family history of type II diabetes mellitus. After an overnight fast, the morning insulin was held and plasma C-peptide levels were drawn. C-peptide levels, which reflect endogenous insulin production, were elevated in all three patients compared with normal controls. Two of the three patients have been able to discontinue the

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Table 1. Characteristics of Pediatric Patients Who Developed IDDM During Switch to FK 506

Patient	Age/Sex	Obese	Family History Diabetes	Liver Disease	Time to Diabetes (d)	Initial Glucose (mg/dL)	Ketones	HLA	C-Peptide (Status)	Current Status	Current HbA1c (%)
1	13/M	No	Type II	CAH	17	367	Negative	Dr3	Present	Off insulin at 9 mo; retransplant 17 mo for recurrent autoimmune hepatitis	4.0
2	13/F	No	None	Crypto cirrhosis	27	1,079	Negative	Dr4	Present	Off insulin at 7 mo	5.4
3	12/M	Yes	Type II	Crypto cirrhosis	21	326	Negative	Dr4	Present	On insulin at 11 mo	9.0

Abbreviation: IDDM, insulin = dependent diabetes mellitus; CAH, autoimmune chronic active hepatitis; HbA1c, Glycosylated hemoglobin (ni: 3.9% to 5.9%).

use of exogenous insulin and maintain normoglycemia and a normal glycosylated hemoglobin but one patient still requires twice daily insulin injections up to 11 months after the switch.

DISCUSSION

The immunosuppressive agent FK 506 is a powerful new drug in the armamentarium used to control rejection of transplanted organs. A diabetogenic effect of the drug has been noted in adults; however, there are no reports of the magnitude of this effect in children.

The frequency of developing new onset insulin-requiring diabetes in children treated with FK 506 was low (<2%). This was somewhat higher in the setting of liver rescue (7%). Thus far, no new onset insulin-requiring diabetes has been noted in kidney or heart rescue patients. The data support the emerging profile of a favorable therapeutic margin of this drug especially in the pediatric population. Our observation of liver rescue as a setting of increased risk to develop diabetes is similar to what has been observed previously in adults.⁷ Also, similarly to what has been noted in adults, all three children had evidence of glucose intolerance prior to the switch to FK 506 although none required insulin treatment while on CyA and steroids. Diabetes in the setting of liver rescue occurs late (2 weeks to 1 month) and glucose monitoring should be performed frequently for several weeks after the switch in "rescue" patients, particularly in those with antecedent glucose intolerance, family history of diabetes, or obesity. Patients on rescue protocols should be taught to recognize the symptoms of diabetes and report if these symptoms occur after hospital discharge. If the patient develops diabetes in this setting, they should receive education about increasing testing frequency and insulin adjustments for changes in immunosuppression. Insulin may be re-

quired for long periods of time but patients may be able to suspend the use of exogenous insulin based on results of home monitoring and glycosylated hemoglobin values. The mechanism of diabetes onset in this setting is unclear. It is possible that since FK 506 and CyA are both lipophilic substances and are concentrated in the pancreas,^{8,9} local concentrations of both drugs in the pancreas allow for a negative synergistic inhibition of insulin release.

A synergistic immunosuppressive effect of the two agents used in combination has previously been reported;¹⁰ however, in humans their combined effects have been too toxic to allow combination of these two agents. The absence of ketonuria and presence of high measurable C-peptide levels in our patients suggest a component of insulin resistance for which the islets cannot compensate. It will be of interest to study the effects of this drug when used as a single agent on insulin secretion and insulin action.

REFERENCES

1. Leonard DK, Landry AS, Sollinger HW, et al: Diabetes 38:172, 1989
2. Tze WJ, Tai J, Cheung S: Transplantation 49:1172, 1990
3. Carroll PB, Boschero AC, Li MY, et al: Transplantation 51:275, 1991
4. Strasser S, Alejandro R, Todo S, et al: Transplant Proc 23:756, 1991
5. Calne R, Collier D St J, Thiru S: Transplant Proc 19:53, 1987
6. Miele L, Todo S, Fung JJ, et al: Transplant Proc 22:41, 1990
7. Miele L, Gordon RD, Mintz DM, et al: Transplant Proc 23:949, 1991
8. Niederberger W, Lemaire M, Maurer G: Transplant Proc 15:2419, 1983
9. Venkataramanan R, Jain A, Cadoff E, et al: Transplant Proc 22:52, 1990
10. Zeevi A, Duquesnoy R, Eiras G, et al: Transplant Proc 19:40, 1987