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Reversibility of Tacrolimus-Induced Posttransplant Diabetes: An Illustrative Case and Review of the Literature

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TACROLIMUS is a potent immunosuppressive agent. It has been reported to have superior immunosuppressive efficacy when compared with the standard formulation of cyclosporine (CyA),[1] based on its ability to rescue patients with failing allografts under CyA-based therapy,[2,3] lower rejection rates when used as a primary immunosuppressive agent,[4,5] and longer projected half-life.[6] However, there have been reports of an increased incidence of posttransplant diabetes (PTDM) under tacrolimus-based therapy.[4,5] We have reported on the reversibility of tacrolimus-induced PTDM in our own renal transplant patients.[7,8] In this article, we present an illustrative case demonstrating the reversibility of PTDM and review both the published and unpublished literature. The data suggest that the initial incidence of PTDM in the renal transplant population may be higher under tacrolimus than under CyA-based therapy, but the final incidence is comparable.[9–11]

ILLUSTRATIVE CASE

The patient was a 64-year old black female with end-stage renal disease secondary to hypertension, who received a kidney from her son. The allograft functioned immediately, and she never experienced rejection. Her serum creatinine, tacrolimus dosages and levels, prednisone dosages, fasting blood glucose levels, and insulin requirements are shown in Table 1. Basically, she was normoglycemic until 13 weeks after transplantation, when her fasting blood glucose level was 280 mg/dL. One week later, it was 555 mg/dL, and she was admitted to the hospital and started on insulin. As her tacrolimus and steroid dosages were tapered, her blood sugars normalized, and her insulin was tapered off by 26 weeks after transplantation. She continues to have normal renal function 1.5 years after transplantation, with a serum creatinine of 1.0 mg/dL, on tacrolimus 1 mg orally twice per day and no prednisone. Her tacrolimus level is 8.7 ng/mL, and her fasting blood glucose is 140 mg/dL.

Review of the Literature

The initial and final incidences of PTDM in various studies of tacrolimus in renal transplantation are summarized in Table 2. The initial incidence ranged from 6% to 28.3%, and the final incidence ranged from 1.4% to 12.6%, with a reversibility of 37% to 83%.[1,4,5,12–15] Subgroup analysis was performed in only one study, the American Phase III Multicenter Trial. It showed a higher incidence of PTDM in African American than in Caucasian

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Table 1. Illustrative Case of Reversible Posttransplant Diabetes (PTDM)

Time	Serum Creatinine (mg/dL)	Tacrolimus Dose (mg/dL)	Tacrolimus Level (ng/mL)	Prednisone Dose (mg/d)	Fasting Blood Glucose (mg/dL)	Insulin (NPH/Reg.) (units/d)
1 week	0.9	20	35.4	20	101	0
1 month	1.1	20	16.3	15	106	0
2 months	1.3	18	18.7	10	115	0
3 months	0.9	16	14.5	10	280	0
14 weeks	1.2	14	16.7	7.5	555	0
16 weeks	1.0	10	10.1	5	186	25/5
18 weeks	1.0	9	13.8	5	152	25/5
20 weeks	1.0	7	6.3	2.5	131	20/0
22 weeks	0.9	5	9.3	0	130	15/0
24 weeks	0.9	5	6.7	0	126	10/0
26 weeks	1.0	5	6.8	0	98	0
8 months	1.0	5	7.9	0	117	0
12 months	0.9	3	11.1	0	148	0
18 months	1.0	2	8.7	0	140	0

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Table 2. Tacrolimus-Associated Posttransplant Diabetes (PTDM) in Kidney Transplantation

Trial	Incidence	Final	Reversibility
American Multicenter Phase III	19.9%	12.6%	37%
Pittsburgh			
Adult*	18%	9%	50%
Children	10%	1.4%	86%
Japan			
Phase II	28.3%	4.7%	83%
Phase III	19.3%	11.1%	42%
European Multicenter Phase III	6%	2.5%	58%

*Randomized trial of tacrolimus/prednisone vs tacrolimus/prednisone/azathioprine.

recipients, and an association in all patients with higher tacrolimus levels and steroid doses.[4,5]

DISCUSSION

The diabetogenicity of tacrolimus appears to be related to a reversible effect of tacrolimus on islet cells. FK binding protein (FKBP) is present in islet cells, and decreased insulin transcription and secretion have been demonstrated experimentally.[16,17] This decrease in secretion is reversible when tacrolimus is discontinued. The direct islet toxicity can explain both the clinical phenomenon of PTDM and its reversibility with dose reduction. The final incidence of PTDM in patients receiving tacrolimus-based immunosuppression is not different than that reported under CyA-based immunosuppression.[9-11] The reversibility is related to reducing both the tacrolimus and the steroid doses. The relatively lower reversibility in the American Phase III Multicenter Trial is probably related to a protocol-driven minimum dose of prednisone in that trial.[4,5]

Given the improved immunosuppressive efficacy associated with tacrolimus,[1-6] the transiently increased incidence of PTDM may well be considered clinically acceptable. Certainly, the potential for PTDM has not prevented the successful use of tacrolimus in kidney/pancreas transplantation, where a number of reports have described its efficacy.[18,19]

When PTDM does occur under tacrolimus-based therapy, it is important not to reduce the dosage too quickly because acute rejection can occur. A gradual reduction in both tacrolimus and steroids will allow continued good graft function, and can lead to a normalization of blood sugars with the eventual discontinuation of insulin.

In summary, while PTDM is a potential complication of tacrolimus, it is often reversible with dosage reduction of both tacrolimus and steroids. The final incidence of PTDM is not different than that reported under CyA-based immunosuppression. Thus, the concern about PTDM should not deter physicians from using tacrolimus-based therapy for their patients.

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