TRANSPLANT INTERNATIONAL

LETTER TO THE EDITORS

Insulin independence after conversion from tacrolimus to cyclosporine in islet transplantation

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Dear Sir,

Today Clinical islet transplantation is an established therapy for a highly selected subgroup of patients with type 1 diabetes mellitus. At our center, C-peptide negative patients with very poor diabetes control including severe hypoglycemia and glycemic lability being refractory to conventional treatment are eligible for islet transplantation. Between 2000 and 2011, the Nordic network has purified 1,742 pancreas and 111 patients have received 286 islet infusions.

Although there has been a steady improvement in immunosuppressant regimen, recipient and donor criteria, islet isolation technique, and infusion procedures, not all patients achieve insulin independence and even if they do, it is often temporary [1]. On the other hand, the wide majority have sustained benefits with less hypoglycemic episodes, better HbA1c levels and restoration of hypoawareness [2]. Even without insulin independence, islet transplantation can reverse and stabilize secondary microvascular diabetic complications [3], and improve renal function after previous kidney transplantation [4].

Most centers use a combination of tacrolimus and mycophenolate mofetil as maintenance immunosuppression in islet transplantation, and in recent years, the use of cyclosporine is limited. Calcineurin inhibitors are diabetogenic and tacrolimus is associated with a higher incidence of new-onset diabetes after transplantation compared with cyclosporine [5]. We present a case where conversion from tacrolimus to cyclosporine resulted in insulin independence.

A 50-year-old Caucasian woman who was diagnosed with type 1 diabetes at 13 and diagnosed with an attention-deficit hyperactivity disorder in adulthood, treated with the psychostimulant methylphenidate was referred to our center. She exhibited severe metabolic instability with in average two severe hypoglycemic incidents a month including unawareness and glycemic lability (Clarke score 7). Insulin requirement was 35 U/day (0.66 U/kg/day); HbA1c 7.0 mmol/mol C-peptide, GAD, IA2 and PRA negative and BMI 19.4.

In 2011, the patient underwent a single islet transfusion from one pancreas with 378 804 IEQ (7134 IEQ/kg) through a percutaneous portal catheter. Induction therapy was given with 3-day infusion of thymoglobuline (1.5 mg/kg) and a TNF-α antagonist (total dose 125 mg). Maintenance immunosuppression consisted of tacrolimus and mycophenolate mofetil 1 g BID.

Four months after the islet transplantation, the patient reported progressive difficulties in walking, muscle stiffness, impaired balance, tremor, and loss of automatic movement of the legs. Examination by a neurologist showed normal reflexes and normal muscle tonus, but sensory impairment. Computer tomography and magnetic resonance imaging of the brain were normal. Neurography showed signs of a mixed sensory and motor polyneuropathy. The symptoms aggravated, although we performed adjustments of concomitant psychostimulating medication and reduced trough levels of tacrolimus from an average of 12–7 μg/l. After repeated examination by a neurologist who could not rule out adverse effect of prescribed medication in combination with pre-existing diabetic neuropathy, we converted the patient from tacrolimus to cyclosporine in October 2011. After conversion, we monitored the patient with abbreviated cyclosporine AUC (3 point measurement 0, 2, and 3 h) being more adequate than C0 or C2 [6]. Initially, we aimed the AUC at 7 000 μg/l and lowered the aim a month later to 5000 μg/l. Fasting C-peptide levels and insulin dose from the day of transplantation until latest review are shown in Fig. 1. Insulin was self-administered and before the switch increased doses suppressed the C-peptide levels. Eighty-8 days after conversion, the patient became insulin independent. At the latest review, the patient reported no severe hypoglycemia and laboratory results showed good metabolic control with an HbA1c 43 mmol/mol and random glucose variation between 5.4 and 7.9 mmol/l.

All the conventional maintenance immunosuppressant agents used in clinical islet transplantation are effective, but at the same time they are nephrotoxic, diabetogenic, or toxic to the beta-cell. In vitro and in vivo studies have shown that tacrolimus, mycophenolate mofetil, and sirolimus in clinically relevant doses impair glucose-stimulated insulin secretion [7]. Sirolimus and tacrolimus have been shown to prevent spontaneous beta-cell proliferation after injury [8].

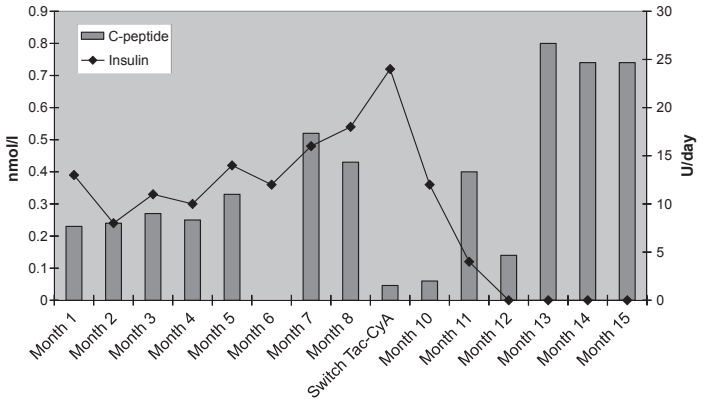

Figure 1 Fasting C-peptide levels nmol/l (gray bars) and insulin dose U/day (line with black diamonds) after islet transplantation. Two seventy-six days after transplantation converted from tacrolimus-based maintenance immunosuppression to cyclosporine, and thereafter insulin independent after 88 days.

The target cell for calcineurin inhibitors is the T-cell where they bind to cytosolic proteins. Cyclosporine binds to cyclophilin and tacrolimus binds to a FK binding protein. The negative effects of calcineurin inhibitors on glucose metabolism are primarily as a result of a decreased pancreatic beta-cell insulin secretion and not because of increased insulin resistance [9], but the primary mechanism still remains unclear. Studies on beta-cells have proposed several actions of both cyclosporine and tacrolimus showing impaired insulin secretion, decreased insulin content of the beta-cell, and impaired insulin transcription [10]. The incidence of new-onset diabetes after kidney transplantation has been shown in the United States Renal Data System to be higher with tacrolimus compared with cyclosporine, but nevertheless associated with improved graft survival [5].

To reduce beta-cell toxicity, there are case reports with switch from tacrolimus to mycophenolate mofetil, driven by neurological side effects with an almost immediate improvement in glycemic control and also an improved response to stimulation testing [11]. In our case, the neurological symptoms partially remained, but we could achieve insulin independence. One might consider an even lower tacrolimus exposure (3–6 μg/ml) would have achieved the same effect, but there was no tendency of lower insulin requirement with the presented dose reduction. Even if there was an 88-day delay before insulin independence, the glycemic control improved immediately after the switch suggesting the more pronounced tacrolimus-induced beta-cell toxicity in comparison with cyclosporine after islet transplantation.

In conclusion, this case report shows remission of beta-cell toxicity after conversion from tacrolimus to cyclosporine. There are ongoing calcineurin-free trials, for example with beletacept and efforts to induce immune tolerance, but meanwhile in selected cases, one might consider cyclosporine as an alternative to tacrolimus in clinical islet transplantation.

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Conflict of interest

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