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Improved Glucose Tolerance in a Kidney Transplant Recipient With Type 2 Diabetes Mellitus After Switching From Tacrolimus To Belatacept: A Case Report and Review of Potential Mechanisms

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Abstract: The introduction of immunosuppressant belatacept, an inhibitor of the CD28-80/86 pathway, has improved 1-year outcomes in kidney transplant recipients with preexistent diabetes mellitus and has also reduced the risk of posttransplant diabetes mellitus. So far, no studies have compared a tacrolimus-based with a belatacept-based immunosuppressive regimen with regard to improving glucose tolerance after kidney transplantation. Here, we present the case of a 54-year-old man with type 2 diabetes mellitus who was converted from belatacept to tacrolimus 1 year after a successful kidney transplantation. Thereafter, he quickly developed severe hyperglycemia, and administration of insulin was needed to improve metabolic control. Six months after this episode, he was converted back to belatacept because of nausea, diarrhea, and hyperglycemia. After switching back to belatacept and within 4 days after stopping tacrolimus glucose tolerance improved and insulin therapy could be discontinued. Although belatacept is considered less diabetogenic than tacrolimus, the rapid improvement of glucose tolerance after switching to belatacept is remarkable. In this article, the potential mechanisms of this observation are discussed.

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Kidney transplant recipients who have preexistent diabetes mellitus (DM) or who develop DM after transplantation (posttransplant DM [PTDM]) have a worse survival and suffer from more cardiovascular morbidity than those without.[1-3] The calcineurin inhibitors (CNI), cyclosporine A (CsA) and tacrolimus, may decrease insulin secretion and increase insulin resistance.[4] The latter is characterized by a decreased insulin sensitivity, that is, more insulin is needed to maintain serum glucose within the reference range.[5]

Belatacept, an inhibitor of the CD28-CD80/86 pathway,[6] does not induce hyperglycemia nor PTDM. Despite the higher acute rejection risk observed in belatacept-treated patients,[7-9] it improves 1-year allograft survival and renal function in kidney transplant recipients with preexistent DM compared with CsA-treated patients.[3]

In addition, belatacept-based therapy decreases the risk of developing PTDM. A meta-analysis which included 729 belatacept-treated and 320 CsA-treated patients showed a relative risk of 0.61 (95%-confidence interval, 0.40-0.93) to develop PTDM with belatacept compared to CsA.[10] Tacrolimus is, nowadays, the most widely used CNI, and treatment with tacrolimus carries a higher risk of developing PTDM than CsA.[11,12]

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Belatacept may be a therapeutic option for kidney transplant recipients that develop PTDM or for those with preexistent DM who develop worsening of metabolic control after starting a CNI-based regimen. Glucose metabolism has not been compared between belatacept- and tacrolimus-treated patients. In addition, no data on the safety and efficacy regarding insulin sensitivity of conversion from CNIs to belatacept after kidney transplantation have been reported.

Here, a kidney transplant recipient with DM is described, who after conversion from belatacept to tacrolimus developed severe hyperglycemia. Glucose control was difficult and did not improve despite high doses of insulin. Within 4 days after stopping tacrolimus and reintroducing belatacept, a marked improvement of glucose tolerance was observed. The purpose of this case report is to discuss the possible pathophysiologic mechanisms explaining this observation and the role of immunosuppressive therapy therein.

CASE DESCRIPTION

A 54-year-old white man received a preemptive, living-unrelated donor kidney transplant in October 2013 because of hypertensive and diabetic nephropathy. His medical history included hypertension since 1992; type 2 DM since 2002; and since 2008, histologically confirmed diabetic and hypertensive nephropathies. The transplant was 2-2-1 mismatched (for HLA-A, HLA-B, and HLA-DR, respectively). Peak and actual panel reactive antibodies were 0%.

The patient was treated with belatacept according to the less-intensive regimen of the Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression trials during the first posttransplantation year as part of a randomized-controlled trial.[13,14] This trial compared belatacept with tacrolimus, and its main findings were described previously.[14,15] In addition to belatacept, he also received induction therapy with 20 mg/kg basiliximab (days 0 and 4) and maintenance therapy with mycophenolate mofetil (targeted to predose concentrations of 1.5-3.0 mg/mL), and prednisolone, tapered to 5 mg/d by month 3 and maintained at 5 mg/d thereafter (Figure 1). The clinical course of the first posttransplant year was uneventful. Belatacept was not reimbursed by the health insurance companies in the Netherlands at the time the patient was 1 year after transplantation (October 2014). Belatacept was discontinued, and he was switched to tacrolimus (Advagraf; Astellas Pharma, Tokyo, Japan) targeted to predose concentrations of 5 to 7 ng/mL (Figure 1).

At the time of transplantation, his DM was well controlled: glycated hemoglobin (HbA1c) was 44 mmol/mol with 24 International Units (IU) of long-acting insulin-glargine (Lantus; Sanofi, Paris, France) daily. Before transplantation, he was taken care of by a nephrologist in a local hospital. Initially, his diabetes was managed with metformin only. When his renal function deteriorated, metformin was stopped, and he was started on long-acting insulin. After transplantation and in an attempt to take patient off insulin, he was started on metformin and glimepiride. Insulin-

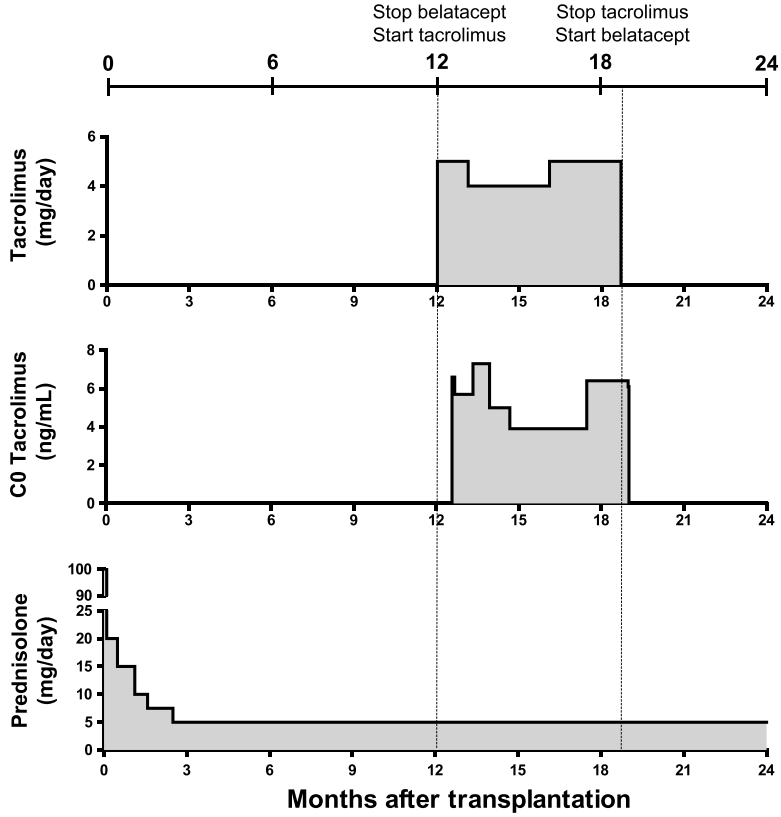

FIGURE 1. Overview of the dose of tacrolimus and prednisolone. The depicted doses of tacrolimus and prednisolone are oral daily doses per time period. Tacrolimus was adjusted to whole blood predose concentrations (C_0). Prednisolone was given as an intravenous dose of 100 mg on days 0 to 3. From day 4 until day 18 the prednisolone dose was 20 mg/d; in weeks 3 to 4 the prednisolone dose was 15 mg/d; in weeks 5 to 6 the prednisolone dose was 10 mg/d; in weeks 7 to 10 the prednisolone dose was 7.5 mg/d; thereafter, prednisolone dose was 5 mg/d. The dashed vertical lines indicate the time points when belatacept was discontinued and restarted.

glargine was initially continued (mean dose, 28 IU/d). In addition, during the first month after transplantation, he received short-acting insulin-aspart (NovoRapid; Novo Nordisk, Bagsværd, Denmark, mean dose 18 IU/d). Four months after his transplantation and when prednisolone had been tapered to 5 mg daily, insulin could be discontinued completely. Figure 2 gives an overview of diabetes-related events, glucose and HbA1c concentrations, and glucose lowering medication. We believe that the combination of improved kidney function, possibly increased physical activity, the introduction of metformin and glimepiride and the tapering of prednisolone to 5 mg daily (Figure 2) allowed for the complete withdrawal of insulin therapy.

Within 14 days after conversion to tacrolimus, the patient developed severe hyperglycemic episodes (Figure 2). Glimepiride and metformin were increased to 6 mg and 3000 mg daily, respectively, without improvement of glucose control (Figure 2). Insulin therapy was restarted (Figure 2). The patient needed up to 50 IU of short- and long-acting insulin on a daily basis to improve metabolic control. Despite the high insulin dose, hyperglycemia persisted. During these hyperglycemic episodes, no infections or changes in bodyweight were observed.

In addition, the patient developed tremors of the hands, nausea, and diarrhea that were all considered as side effects of tacrolimus. Clinically, no signs of tacrolimus-associated nephrotoxicity were observed. No (protocol) kidney biopsy was performed after conversion to tacrolimus. Because of these side effects, 6 months after conversion, belatacept (5 mg/kg bodyweight monthly) was restarted. Tacrolimus was discontinued overnight. Four days after discontinuing tacrolimus, the patient's blood glucose concentrations improved tremendously, and insulin therapy could be stopped. During the 2-year follow-up period, the patient has remained in good clinical condition. No acute rejection

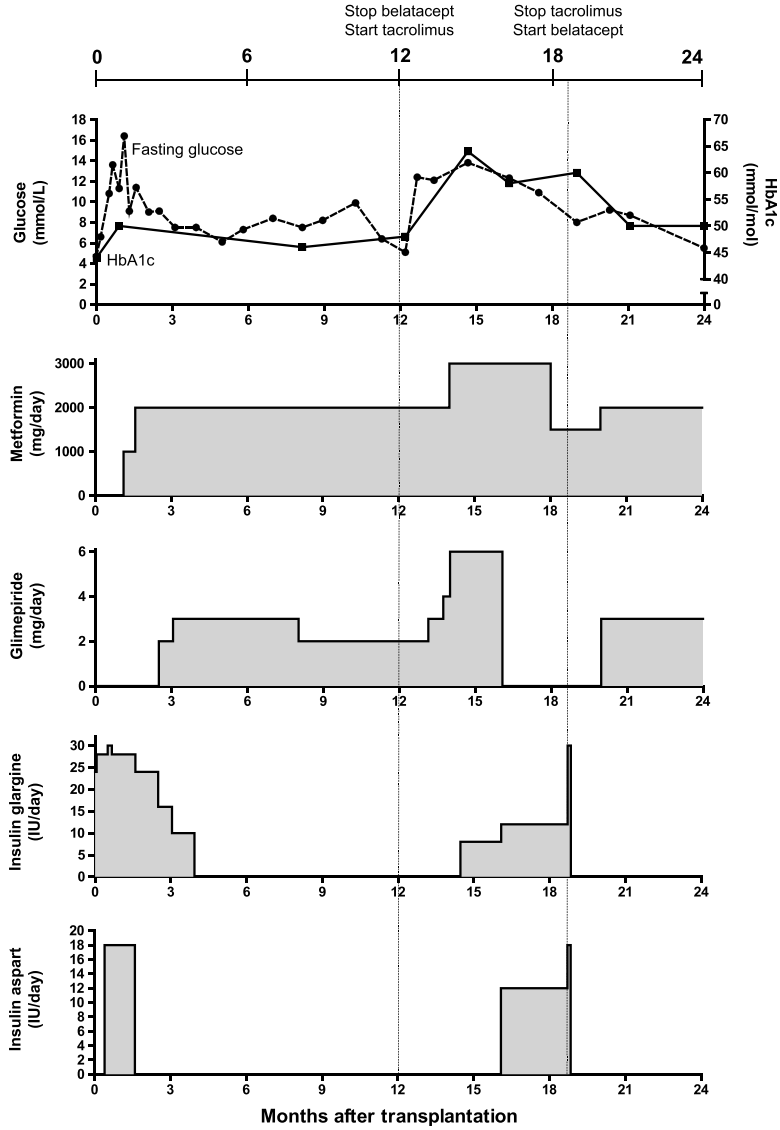

FIGURE 2. Overview of diabetes-related events, measurements, and glucose-lowering medication. A timeline is depicted, indicating important events related to changes in glucose concentrations. The presented glucose and HbA1c concentrations were measured in hospital at the outpatient clinic. The maximum target concentration of HbA1c was 53 mmol/mol. Glucose concentrations measured at home are not included. The daily doses per period are given for metformin, glimepiride, insulin-glargine, and insulin-aspart. From days 12 to 48 after transplantation, doses of insulin-aspart were adjusted to target a premeal glucoses concentration of <10 mmol/L (average dose was 18 IU/d). The dashed vertical lines indicate the time points when belatacept was discontinued and restarted.

occurred, and his eGFR has remained stable (55 mL/min per 1.73 m^2; **Figure S1,** http://links.lww.com/TXD/A63). His current glucose-lowering treatment consists of metformin and glimepiride.

DISCUSSION

In this patient, a marked improvement in glucose tolerance was observed after switching from belatacept to tacrolimus. Improvement of glucose control occurred immediately after withdrawal of tacrolimus and exogenous insulin could be stopped within 4 days. The improvement in glucose was not related to changes in BMI (**Figure S1,** http://links.lww.com/TXD/A63). Although it is well known that belatacept is less diabetogenic than CNIs,[10] the rapid improvement of glucose tolerance was remarkable and unexpected.

Tacrolimus may induce DM by several mechanisms. First, tacrolimus reduces insulin secretion by the pancreatic β cells via decreasing insulin mRNA expression through inhibition of 2 pathways (nuclear factor of activated T cells and cAMP response element-binding protein).[16-19] Second, the insulin content of the β cell is diminished by tacrolimus.[17] Third, the glucose-induced insulin release is inhibited by tacrolimus through reduced glucokinase activity.[17,20] Fourth, tacrolimus directly induces β cell apoptosis and reduces islet cell proliferation.[19,21] Altogether, these effects lead to a reduction of insulin secretion. Furthermore, CNIs may induce insulin resistance by stimulating endocytic removal of glucose transporter type 4 (Glut-4) from the cell membrane of adipocytes and muscle cells.[22]

The induction of hypomagnesemia is another mechanism by which tacrolimus may directly influence glucose tolerance.[23] Tacrolimus can downregulate the magnesium absorbing channel transient receptor of potential melastatin (TRPM6) in the distal collecting tubule and thereby induce hypomagnesemia via renal magnesium wasting.[24] Hypomagnesemia may contribute to insulin resistance by decreasing autophosphorylation of the β subunits of the insulin receptor.[25] Besides, hypomagnesemia may reduce insulin secretion.[25] Unfortunately, it is unknown if hypomagnesemia played a role in our case, because magnesium concentrations were not measured.

We think that the fast improvement of glucose control after switching to belatacept in our patient was mainly related to (1) the discontinuation of tacrolimus and/or (2) a direct effect on insulin resistance by CD80-86 blockade by belatacept. Several animal studies have described the effects of discontinuation of tacrolimus on glucose metabolism. Redmon et al[17] observed reversibility of insulin secretion 72 hours after discontinuation of tacrolimus in hamster β-cells (HIT-T15). Another in vitro study using rat β cells found similar results.[26] In an in vivo study, reversibility of rat β cells insulin gene expression, insulin content, and insulin secretion was observed 7 days after discontinuing tacrolimus.[27] Another study in rats showed that the insulin resistance improved 5 days after the last dose of tacrolimus.[28]

All these studies show reversibility of impaired glucose tolerance after discontinuation of tacrolimus. However, these studies are limited by the short duration of tacrolimus treatment. Prolonged administration could possibly lead to a more severe reduction of functional β-cell mass and irreversibility of impaired glucose control. Furthermore, to the best of our knowledge, no studies in humans have analyzed directly the effects of insulin secretion and resistance after discontinuation of tacrolimus. Boots et al[29] described the effect of tacrolimus dose reduction on insulin secretion. In 15 kidney transplant recipients without DM, a 33% reduction in the tacrolimus predose concentrations resulted in a 36% increase in β cell secretion capacity.[29]

The fast improvement of glucose tolerance in this case may also have been caused by the introduction of belatacept (rather than the withdrawal of tacrolimus). One study has suggested that CD86 may play a role in insulin resistance via interaction with the adiponectin axis.[30]

Interestingly, a case report of a patient with rheumatoid arthritis reported an improvement of insulin resistance 4 weeks after treatment with abatacept, which is considered a lower-affinity version of belatacept.[31] In another study, improved insulin sensitivity was observed in 15 patients 6 months after the start of abatacept treatment.[32]

In contrast to the findings of the studies described above, Zhong et al[33] found in mice and humans that a higher CD80/86 expression was negatively correlated with insulin resistance. No effect of adiponectin on CD80/86 expression was noted on human macrophages in another study.[34]

The main limitation of this case report is that the mechanistic evidence of the effect of belatacept and tacrolimus on glucose tolerance is lacking. We did not examine endogenous insulin secretion and insulin resistance.

In conclusion, a kidney transplant recipient with preexisting type 2 DM is described who showed a rapid improvement of glucose tolerance after switching from tacrolimus to belatacept. Such a strategy may be beneficial in comparable cases although high-quality evidence of the safety of this intervention in terms of rejection is currently lacking.

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