

Conversion from tacrolimus to belatacept to prevent the progression of chronic kidney disease in pancreas transplantation: case report of two patients

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ABSTRACT

Belatacept is a novel immunosuppressive agent that may be used as an alternative to calcineurin inhibitors (CNI) in immunosuppression (IS) regimens. We report two cases of pancreas transplant that were switched from tacrolimus (TAC) to belatacept. Case 1: 38-year-old female with pancreas transplant alone maintained on TAC-based IS regimen whose serum creatinine (SCr) slowly deteriorated from 0.6 mg/dL at baseline to 2.2 mg/dL, 16 months posttransplant. A native kidney biopsy performed showed CNI toxicity. The patient was started on belatacept and TAC was eliminated. Case 2: 49-year-old female with simultaneous pancreas–kidney transplant, maintained on TAC-based regimen where the SCr worsened over an initial 3-month period from a baseline of 1.0 to 3.0 mg/dL. Belatacept was started and TAC was lowered. Due to persistent graft dysfunction and kidney transplant biopsy still showing changes consistent with CNI toxicity, the TAC was then discontinued. At >1 year postbelatacept and off TAC follow-up, kidney function as measured by SCr remains stable at 1.0 ± 0.2 mg/dL in both recipients. Neither patient developed rejection following the switch, and pancreas allograft function remains stable in both recipients.

ABBREVIATIONS

CAN: chronic allograft nephropathy

CKD: chronic kidney disease

CNI: calcineurin inhibitors

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DM: diabetes mellitus

DSA: donor-specific antibody

EBV: Epstein–Barr virus

FBG: fasting blood glucose

GFR: glomerular filtration rate

IS: immunosuppression

MMF: mycophenolate mofetil

PAS: periodic acid-Schiff

PRA: panel reactive antibodies

PTA: pancreas transplantation alone

SCr: serum creatinine

SPK: simultaneous pancreas–kidney transplant

SRL: sirolimus

TAC: tacrolimus

UPr/UCr: random urine protein to urine creatinine ratio

Keywords: *Clinical research/practice, immunosuppression/immune modulation, kidney transplantation/nephrology, pancreas/simultaneous pancreas–kidney transplantation, off-label drug, use patient safety.*

INTRODUCTION

The calcineurin inhibitors (CNI), cyclosporine and tacrolimus (TAC), continue to be the primary agents used as a part of immunosuppression (IS) regimens for nearly all types of solid organ transplantations [1-3](#). Low rejection rates, as well as excellent graft and patient survival rates have been observed following the introduction of these agents. However, one of the drawbacks to CNI therapy is their propensity to cause chronic nephrotoxicity leading to interstitial fibrosis and tubular atrophy. There are many potential mechanisms aside from vasoconstriction, and pathologic changes from CNI in the transplanted kidney are observed as early as 1 year. These changes increase remarkably in the years following transplantation and contribute to fibrosis, atrophy and transplant glomerulopathy eventually leading to graft loss [4, 5](#).

Unlike the kidney, the pancreas is highly immunogenic and associated with a high risk of rejection especially among nonuremic recipients of pancreas transplantation alone (PTA) [6](#). This has led to the use of regimens with higher concentrations of CNI [3, 7](#). Belatacept, the first selective T cell costimulation blocker approved to prevent acute rejection in adult renal transplant recipients does not cause nephrotoxicity. Recent studies comparing regimens in which belatacept was used to either replace or reduce the dose of the CNI have shown success in low risk kidney transplant recipients [8, 9](#). Furthermore, switching patients maintained on a CNI-based regimen to a belatacept-based regimen was shown to be effective in preventing the progression of kidney allograft dysfunction from CNI toxicity [10](#).

There have been no published reports describing the use of belatacept to prevent the progression of chronic kidney disease (CKD) in pancreas transplant recipients or its use as a primary IS regimen in pancreas transplantation. In this report, we describe our experience of converting TAC to belatacept in two pancreas transplant recipients to preserve renal function.

CASE PRESENTATION

Case 1: pancreas transplant alone

A 38-year-old female with a history of chronic pancreatitis and type 1 diabetes mellitus (DM) following a total pancreatectomy underwent a PTA for recurrent hypoglycemic unawareness episodes. At the time of transplant, the patient had normal kidney function (serum creatinine [SCr] 0.8 mg/dL, undetectable proteinuria). The patient's pretransplant Flow panel reactive antibodies (PRA) Class I and Class II were 0. Induction therapy consisted of five doses of antithymocyte globulin (1 mg/kg/dose) and a single dose of rituximab (150 mg/m²). Maintenance IS regimen consisted of a triple drug IS regimen of TAC (target trough level, 8–10 ng/mL), sirolimus (SRL) (target trough level, 3–5 ng/mL) and mycophenolate mofetil (MMF) 500 mg orally twice daily. There were no other nephrotoxic medications and the patient received prophylaxis with valganciclovir and trimethoprim/sulfamethoxazole.

Over a 16-month period posttransplant, the patient had excellent pancreatic allograft function, with a fasting blood glucose (FBG) of 91 mg/dL, A1C 5.6% and serum lipase 20 U/L. A gradual decline in renal function occurred over 6 months with SCr increasing from 0.6 mg/dL at baseline to 2.2 mg/dL. Prerenal causes were excluded and BK virus screening was negative. The mean TAC trough levels at 1, 3, 6, 12, 18 and 22 months were: 7.5, 8.3, 7.9, 8.1, 6.9 and 6.0 ng/mL, respectively. The mean SRL trough levels were 4.0, 3.7, 4.1, 3.1, 3.8 and 4.2 ng/mL, respectively. A native kidney biopsy was performed showing 40 glomeruli being sampled with approximately 25% obsolescence. Overall glomerular size and cellularity were within normal limits. Mesangial matrix lacked diabetic type “KW nodules.” A few glomeruli (~10–20%) showed mild mesangiolytic. Glomerular capillary loop basement membranes were focally wrinkled and thickened. Tubules showed moderate atrophy (~50% of sampled tubules) with some lumina containing cell debris and Tamm–Horsfall protein casts. There was mild interstitial fibrosis and infiltrates of lymphocytes. Arteries show moderate fibrous intimal thickening without onion-skin change. Arterioles showed severe subintimal hyalinosis (Figure 1).

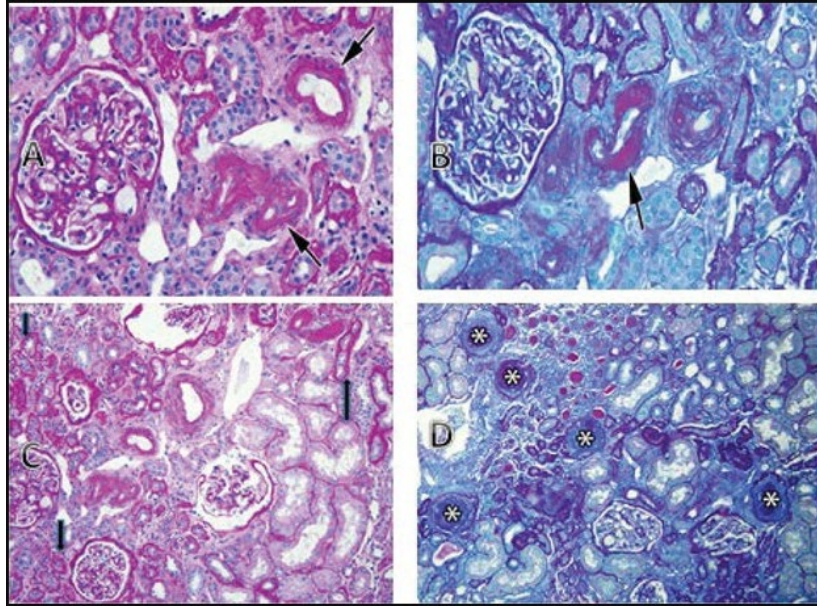


Figure 1: Light microscopic findings of native kidney biopsy in patient with pancreas transplant alone. (A) Periodic acid-Schiff (PAS) stain: arrows indicate hyaline arteriosclerosis in a background of moderate tubular atrophy. (B) Allochrome stain from the same field but deeper level of sectioning. Arrow indicates hyaline arteriosclerosis in a background of mild interstitial fibrosis. (C) PAS stain: striped pattern of fibrosis and tubular atrophy. (D) Allochrome stain: asterisks indicate glomerular obsolescence.

After screening to ensure the patient was Epstein–Barr virus (EBV) IgG positive, belatacept therapy was initiated. Belatacept was administered as 5 mg/kg dose via intravenous infusion on days 1, 15, 29, 42, 57 and then every 28 days thereafter [10](#). The TAC dose was gradually reduced by 25% each week with complete stop at 4 weeks. No changes were made in SRL target levels and maintained between 3 and 5 ng/mL. Following conversion, there was a gradual improvement in SCr (Figure [2](#)). Labs from the last follow-up visit which was 17 months postconversion showed SCr of 1.0 mg/dL, random urine protein to urine creatinine ratio (UPr/UCr) 0.18, A1C 5.7%, FBG 98 mg/dL, serum lipase 23 U/L and C-peptide 2.9 ng/mL. HLA donor-specific antibody (DSA) and anti-insulin autoantibodies were undetectable, and serum EBV and BK virus remain negative.

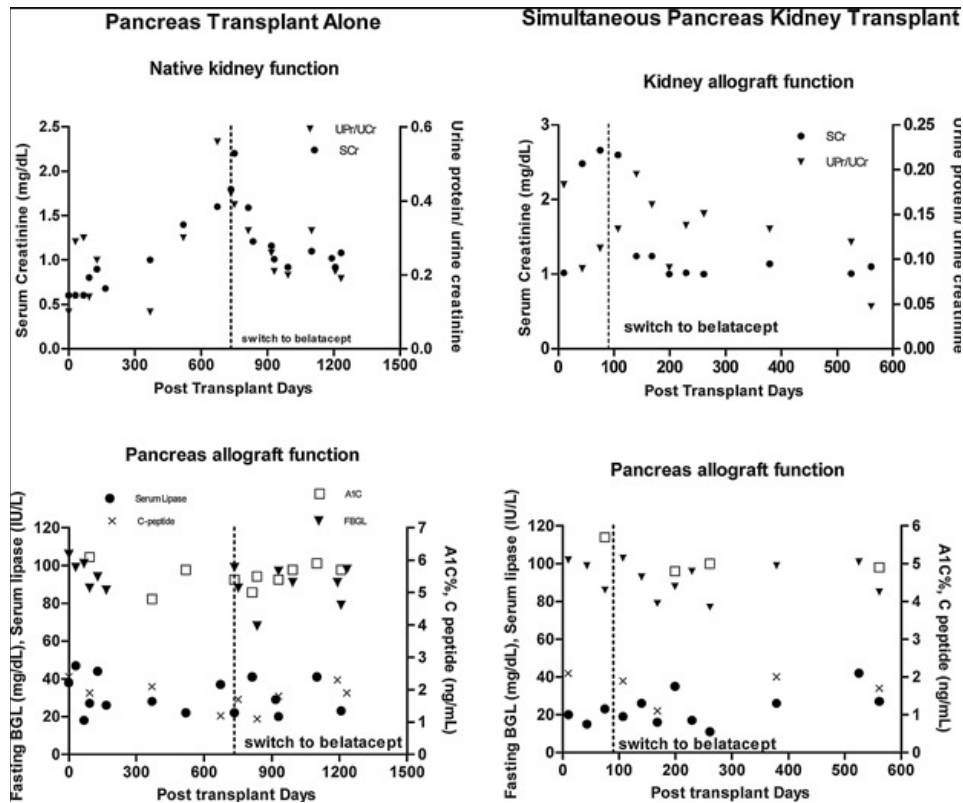


Figure 2: Kidney and pancreas function over time. Dotted line indicates switch from tacrolimus to belatacept. Mean SCr, serum creatinine; UPr/UCr, random urine protein to urine creatinine ratio; BGL, blood glucose levels. Same symbols are used to depict the variables.

Case 2: Simultaneous pancreas–kidney transplant

A 49-year-old female with history of insulin dependent DM, undetectable fasting C-peptide levels, hypoglycemic unawareness and end-stage renal disease with a prior failed kidney transplant underwent a zero antigen mismatch simultaneous pancreas–kidney transplant (SPK). Her other co-morbid conditions included, mild obesity, peripheral arterial disease, congestive heart failure, hypertension, hyperlipidemia, hypothyroidism, seizure disorder, mild mitral stenosis and mild pulmonary hypertension. The patient was highly sensitized with Class 1 and Class II Flow PRA of 84% and 56%, respectively, and had received desensitization therapy with intravenous immunoglobulin and rituximab while on the waiting list. Induction regimen consisted of five doses of antithymocyte globulin, rabbit (1 mg/kg/dose) and maintenance IS consisted of a combination of TAC (target 12 h trough

level, 8–10 ng/mL) and MMF 1000 mg twice a day. There were no other pertinent nephrotoxic medications and the patient received standard prophylaxis with valganciclovir and trimethoprim/sulfamethoxazole.

The patient's FBG after transplant was 98 mg/dL, A1C 5.6%, C-peptide 1.7 ng/mL, serum lipase 19 U/L. Renal function at 2 weeks posttransplant was normal with SCr 1.0 mg/dL and UPr/UCr of 0.10. Over a period of the next 3 months, the SCr gradually increased to 3 mg/dL. Due to worsening graft function and history of congestive heart failure, diuretics were used during this course. The mean TAC trough levels at 1, 2 and 3 months were 7.5, 8.0 and 6.7 ng/mL, respectively. It was then decided to start her on belatacept and minimize her TAC levels to 2–5 ng/mL. However, graft function remained poor at SCr of 2.6 mg/dL, despite mean TAC levels of 3.3 mg/dL. At 7 weeks into belatacept therapy, a biopsy was performed with 19 glomeruli sampled. It revealed mild tubular necrosis and mild to moderate tubular atrophy with interstitial fibrosis. Arteries showed intimal thickening and arterioles showed subintimal hyalinosis. Glomerular obsolescence was minimal (1/19).

Based on the biopsy results it was then decided to totally eliminate TAC and remain on a regimen of belatacept, MMF and SRL. The TAC dose was gradually reduced by 25% each week with complete stop at 4 weeks. When TAC was discontinued, SRL was initiated (24 h trough level 3–5 ng/mL). The mean SRL trough levels at 1, 3, 6 and 12 months were 4.1, 3.8, 4.3 and 4.4 ng/mL, respectively. Over the next few weeks and months, the graft function improved gradually (Figure 2). One measurement of Immuknow® (Viracor-IBT Laboratories, Lee's Summit, MO) ATP value of 283 ng/mL (moderate immune response range 226–524) was obtained 6 weeks after starting belatacept. The most recent labs obtained 16 months postconversion were SCr 1.0 mg/dL, UPr/UCr 0.09, fasting C-peptide 1.1 ng/mL, FBG 85 mg/dL, serum lipase 19 U/L and A1C 4.7% (Figure 2). DSA and anti-insulin autoantibodies remain undetectable, and serum EBV and BK remain negative.

DISCUSSION

CNI nephrotoxicity can occur despite maintaining CNI trough serum concentrations within the therapeutic range. Nephrotoxicity due to CNI is a clinicopathological entity whose

diagnosis is difficult to establish and sometime can only be confirmed through renal biopsy findings or elimination of CNI. The histological features indicative of acute CNI toxicity are necrosis and dropout of individual myocytes, the onset of replacement of these myocytes with hyaline insudates in afferent arterioles and isometric vacuolation, predominantly in the straight proximal tubules. In chronic toxicity, beaded medial hyalinization of afferent arterioles, striped interstitial fibrosis and tubular atrophy are observed [5](#). However, as CNI nephrotoxicity can overlap with other pathological findings such as acute tubular necrosis, and chronic rejection/chronic allograft nephropathy (CAN), the confirmatory diagnosis usually requires minimization or elimination strategies.

In our cases, the main rationale to switch to belatacept and eliminate TAC was to provide adequate IS for the pancreas transplant while at the same time preserving renal function. Based on the clinical course and biopsy findings, both cases clearly show that the poor renal function was due to TAC therapy. Belatacept has been studied extensively recently in kidney transplant patients [8-12](#). Treatment with belatacept is associated with better renal function, less CAN and an improved cardiovascular risk factor profile compared with cyclosporine. The overall safety profile of belatacept was similar to cyclosporine in the *de novo* setting. However, it has been associated with more severe early acute rejection episodes and an increased risk for posttransplant lymphoproliferative disorder affecting the central nervous system, particularly in those that were EBV IgG seronegative at the initiation of belatacept therapy.

Pancreas transplantation has been increasingly accepted as an intervention to manage labile DM during the last few decades. Survival rates of pancreatic grafts have improved over time [6, 13](#). This may be because of better surgical techniques, but also largely due to reduction in early acute rejection from newer IS regimens [6](#). Pathologic changes from diabetes are frequently seen in native kidneys of PTA. These morphologic lesions of the native kidney disease have also been reported to reverse after PTA [14](#). However, proteinuria and kidney function after PTA remain important risk factors. Preexisting kidney dysfunction (SCr > 1.5 mg/dL), young age at transplantation and high TAC trough concentrations have been identified as risk factors for a decline in kidney function and progression to end-stage renal disease following pancreas transplantation [3, 15](#). An

estimated GFR diminution ranging from 33% to 44% at 5 years has been reported [16](#). Also in SPK, patient survival is more dependent on renal than on pancreas allograft survival [17](#). Hence preserving long-term renal function remains an ultimately very important goal in renal and nonrenal organ transplantation. Conversion to mammalian target of rapamycin inhibitors is attempted in many cases to preserve renal function in kidney transplantation or other nonpancreas organ transplantation [18](#). However, short of nonrandomized single study reports of CNI elimination, there is no data to support safe CNI free IS in pancreas transplantation [19](#).

Our cases do have certain limitations. There are no follow-up biopsies to see if the CNI-induced changes reversed or stabilized as the patients have maintained excellent renal function. We also do not have any tests of T cell reactivity (ELISPOT, ImmuKnow®) serially performed on our cases to further study the immune response in this approach in pancreas recipients. We did not have any formal measurements of GFR through measured urine creatinine clearance or iothalamate studies, thus limiting its efficacy on true graft function. Case 1 had the biopsy performed before conversion to belatacept, while Case 2 had the biopsy performed while TAC was minimized but not eliminated. In Case 2, although the timing of the biopsy was not preconversion, the fact that elimination of TAC significantly improved the graft function back to normal levels supports the diagnosis of CNI-induced nephrotoxicity. It is also possible that there are different cellular and immunological mechanisms in play preventing the pancreas from rejection and this effect may not be solely due to the belatacept maintenance therapy as both patients had received rituximab.

Our reported short-term experience with belatacept therapy in these two patients is encouraging as we did not observe development of postswitch DSA, anti-insulin autoantibodies, infections, posttransplant lymphoproliferative disorder or any clinical evidence of pancreatic allograft dysfunction. In our two cases with unusually rapid deterioration of renal function, stopping the CNI and starting belatacept led to improvement of renal function without evidence of kidney or pancreas rejection. Pancreas rejections can be devastating with potential for necrosis, abscess or enteric perforations and gastro-intestinal hemorrhage. Currently there are ongoing studies using belatacept

in SPK (www.clinicaltrials.gov; NCT01790594; CTOT 15). Hence, before we can recommend using belatacept to prevent CKD progression in the pancreas transplant population, the authors recommend waiting for such studies or an SPK conversion study be undertaken in a systematic fashion.

DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. M. A. Mujtaba has received an investigator-initiated research grant from Bristol-Myers Squibb. There is no honoraria or salary support. All the other authors have no conflicts of interest to disclose.

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