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Tacrolimus to Belatacept Conversion Following Hand Transplantation: A Case Report

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Abstract

Vascularized composite allotransplantation (VCA) has emerged as a viable limb replacement strategy for selected patients with upper limb amputation. However, allograft rejection has been seen in essentially all reported VCA recipients indicating a requirement for substantial immunosuppressive therapy. Calcineurin inhibitors have served as the centerpiece agent in all reported cases, and CNi-associated complications associated with the broad therapeutic effects and side effects of calcineurin inhibitors have been similarly common. Recently, belatacept has been approved as a calcineurin inhibitor replacement in kidney transplantation, but to date, its use in VCA has not been reported. Herein, we report on the case of a hand transplant recipient who developed recurrent acute rejection with alloantibody formation and concomitant calcineurin inhibitor nephrotoxicity, all of which resolved upon conversion from a maintenance regimen of tacrolimus, mycophenolate mofetil and steroids to belatacept and sirolimus. This case indicates that belatacept may be a reasonable maintenance immunosuppressive alternative for use in VCA, providing sufficient prophylaxis from rejection with a reduced side effect profile, the latter being particularly relevant for nonlife threatening conditions typically treated by VCA.

Introduction

Vascularized composite allotransplantation (VCA) has been introduced as an option for limb replacement and reconstruction of major tissue defects unable to be reconstructed with autologous tissue. To date, over 100 patients have received a VCA worldwide. Most patients are currently maintained on multi-drug regimens typically including a calcineurin inhibitor

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(CNI), mycophenolate mofetil (MMF), and steroids. As such, complications arising from these agents are the most commonly reported posthand transplantation and include renal dysfunction, hyperglycemia, and dyslipidemia (1). Importantly, current regimens do not completely prevent acute VCA rejection or chronic graft loss, and alloantibody-mediated rejection also has been reported (1–3). Furthermore, they require daily administration of several medications, thereby increasing the requirement for strict regimen adherence. The ideal anti-rejection regimen would avoid major toxicities and have lasting control of the alloimmune response. Costimulation blockade offers promise to provide well tolerated prophylaxis from allograft rejection and also has been suggested to have particular control over alloantibody formation (4). Based on our experience with costimulation blockade in kidney transplantation, we applied a costimulation-based immunosuppressive regimen for a hand transplant recipient.

The Recipient

At the time of transplantation, the recipient was a 21-year-old, right-hand dominant female with history of Kawasaki disease diagnosed at the age of 3 months. She progressed with severe vasculitis of the extremities and heart. This necessitated a left knee disarticulation, right below the knee amputation, and left wrist disarticulation at the age of 4 months. The patient ambulates well with lower extremity prostheses, but her ambulatory ability and general activities of daily living were encumbered by her lack of her left hand. After informed consent and extensive preoperative education and evaluation, the patient was included in an Institutional Review Board approved protocol (IRB #00000760, [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00778856) #NCT00778856). Preoperative echocardiographic findings revealed a normal ejection fraction with no stress-induced wall motion abnormalities. The patient's blood type was O+ and she was cytomegalovirus (CMV)+, Epstein–Barr virus (EBV)+, hepatitis B–, and hepatitis C–. Her serum creatinine was 0.50 mg/dL, and her quantitative evaluation of upper extremity function test (5) was 21/99 before the transplant. Panel reactive antibody (PRA) testing was 0% for Class I and 0% for Class II as determined by a flow cytometric-based solid phase HLA antibody detection assay (One Lambda, Inc., Canoga Park, CA) as previously described (6).

The Procedure

The donor/recipient pair was matched for blood type, sex, skin pigmentation, CMV, EBV, and size. The procurement of the limb was performed at the distal forearm. The transplant was performed following the standard of care for major limb replantation (7,8) (Figures 1A–B). The patient received induction with rabbit-anti-thymocyte globulin (RATG) 1.5 mg/kg IV intraoperatively, but developed signs consistent with cytokine release syndrome, necessitating termination of the RATG infusion intraoperatively. RATG was not restarted postoperatively. Intraoperatively, she received 12 units of red blood cells, 6 units of FFP, and 1 unit of platelets. The patient was started on a rehabilitation program during the first week after surgery and was discharged from the hospital on postoperative (POD) day 15.

Postoperative Monitoring

Currently, the patient is 42 months posttransplant. Maintenance immunosuppression postsurgery consisted of tacrolimus dosed to achieve 12-h trough levels between 10 and 15 ng/mL (Figure 2), MMF, 1 gm twice daily and steroids. Skin biopsies were taken at predetermined times and at signs of rejection and scored using the Banff scoring system (9).

A protocol biopsy taken on POD 7 revealed a VCA-Banff I without visual skin changes in the allograft. Her tacrolimus level was 9.3 ng/mL. Screening for HLA-antibody demonstrated a PRA of 27% class I and 0% class II. *De novo* alloantibody specificities to HLA-B* 27, 47, 48, 60, 61 and 81 were identified utilizing a Luminex™-based microparticle assay as previously described (6). Although none of these antibodies were directly donor specific, they were felt to be likely reacting to an epitope shared by the two donor HLA-B* locus antigens (namely B*07 and B*55), that is, the B7 cross reactive group. The patient received prednisone 100 mg PO × 5 days to treat rejection with a rapid taper to 10 mg/day. On POD 90, the patient presented with diffuse round dark pink skin lesions localized to the allograft. Her biopsy showed mild epidermal spongiosis with rare diskeratotic keratinocytes and mild perivascular lymphocyte infiltrate consistent with VCA-Banff I to early VCA-Banff II. Rejection reversed with methylprednisolone 500 mg IV × 3 days with a rapid taper to prednisone 10 mg/day. On POD 129, the patient presented with a cutaneous eruption characterized by coalescent erythematous papules localized to the allograft (Figure 3A). Biopsy of the skin showed a moderate perivascular and perieccrine lymphocytic infiltrate with associated epidermal spongiosis and exocytosis, consistent with VCA-Banff II rejection (Figure 3B). A muscle biopsy at this time showed a focally moderate perivascular lymphocytic infiltrate. Vasculopathy was limited to focal endothelial cell swelling. Vasculitis was not identified in either the skin or muscle biopsy. Immunohistochemistry for C4d was negative in the skin biopsy. She was treated with systemic steroids followed by RATG for 7 days. The rash and follow-up biopsy showed resolution of rejection. Soon after the initiation of tacrolimus and despite the multiple attempts to reduce the CNI level and avoid nephrotoxicity, the patient's creatinine progressively increased to a level of 2.08 mg/dL by year 1 (Figure 4).

During the 1-year study visit, the patient reported being well adjusted to the transplant. Her Carroll test results doubled to 42/99, Tinel's sign was evident at the fingertips, and among other daily activities, she was able to drive and cook with both hands. On examination, the allograft had no visual changes in coloration and no dysfunction as measured by range of motion and sensation. Nevertheless, a protocol skin biopsy of the allograft revealed VCA-Banff I. Immunohistochemistry for C4d was negative. The MRA showed delayed filling of both the radial and ulnar arteries, the palmar arch of the transplanted hand in comparison with the contralateral, and minimal opacification of the digital arteries. This was a distinct change in comparison to the examination 7 months prior. Ultrasound Doppler showed consistently decreased velocities in the allograft arteries compared to the same vessels in the right arm. The HLA antibodies present at this date were specific for HLA-B*48, 60, 61, and 81, which, again, while not directly donor-specific, likely recognized a shared epitope expressed by the donor's mismatched HLA-B* locus antigens. A diagnosis of antibody-mediated rejection was made and the patient was treated with IVIG and plasmapheresis. At

this time, due to the patient's intolerance to CNIs and the emergence of possible donor-specific HLA antibodies the patient was started on belatacept intravenous (IV) monthly and sirolimus aiming at trough levels of 8–12 ng/mL. MMF and tacrolimus were discontinued. Prednisone was continued at 5 mg QD. Her renal function improved and no further episodes of rejection were seen.

Currently, the patient is on belatacept 350 mg every 8 weeks without side effects, sirolimus 3 mg QD with a trough level of 6.5 ng/mL and prednisone 5 mg QD. Her serum creatinine is 0.92 mg/dL, and her allograft function continues to improve. She has initiated guitar classes, is playing golf, and is hitting balls with a baseball bat (Figures 5A and B). Electrodiagnostic studies show small sensory response for the median nerve and normal conduction velocity during the ulnar motor study. She has mild ongoing denervation changes only in the first dorsal interossei (FDI) with reduced recruitment in the ulnar innervated muscle, and single motor unit in the median nerve innervated muscle (abductor pollicis brevis), representing preservation of axonal continuity. After the transplant, vascular studies showed the allograft radial and ulnar arteries with velocities usually in the 30 s compared to 40–90 s in the native arteries. The 2013 examination is the exception with increased velocities in the allograft arteries at the wrist. The intimal media thickness was measurable in the allograft arteries but did not increase during the time frame. Intimal medial thickness (IMT) remained 0.06 or less. She has shown no signs of rejection either visual or by histology after the initiation of belatacept.

In our case, after 30 months on belatacept, the patient has tolerated the initial monthly and currently every-2-months doses without signs of rejection after the conversion. Results, to date, include serum creatinine, 0.92 mg/dL, GFR >70, WBC 8.5×10^3 , total cholesterol 171 mg/dL, HDL 52 mg/dL, LDL 53 mg/dL, triglycerides 328 mg/dL. DSA are undetected and her antibody pattern has not changed compared to previous samples. Her allograft function has not been impaired. She remains on sirolimus 3 mg QD (latest trough level was 11.3 ng/mL), and prednisone 5 mg a day. Other medications are aspirin and pravastatin indicated for her Kawasaki disease. Her last skin biopsy at 17 months on belatacept showed Banff 0 and C4d-nonreactive (Figure 6). Urinalysis showed a trace of proteinuria.

Discussion

Vascularized composite allotransplantation has emerged as a viable limb replacement strategy for selected patients with upper limb amputation. The centerpiece agent reported in all VCA cases is CNIs and the largest number of complications in VCA recipients has been secondary to the use of CNIs and steroids. These include hyperglycemia, end-stage renal disease, increase creatinine levels, Cushing syndrome, avascular necrosis of the hip, and hyperparathyroidism (1). These complications loom particularly large given the nonlife-saving nature of VCA.

Recently, belatacept was approved as a CNI replacement in kidney transplantation. Belatacept is a fusion protein between a modified extracellular domain of CD152 and human IgG1 (9). Belatacept, its parent molecule CTLA4-Ig and other biologics specific for the B7 costimulatory molecules have been studied extensively *in vitro*, in NHPs and in clinical trials

by our group and others (10–16). Belatacept is a first-in-class selective costimulation blocker and is clinically indicated as a CNI inhibitor substitute with mycophenolate mofetil and steroids after renal transplantation. Studies in murine models have showed synergy between costimulation blockade and mTOR inhibitors (17). Studies in nonhuman primates have demonstrated that the combination of belatacept and sirolimus prolong renal and islet allografts survival (18,19), and we have demonstrated a therapeutic effect in NHP VCAs (data not shown). Clinically, Phase III trials have shown supremacy of belatacept in the conservation of renal function and other adverse events compared to CNIs (4).

Our patient started with RATG during surgery, which required premature termination. It is reasonable to assume that the patient's induction was suboptimal. After careful consideration and watchful observation, the patient received RATG to treat the rejection episode on POD 129 and presented with another rejection episode at her 1-year study visit. She was placed on CNIs for the potential additional benefit of tacrolimus on accelerating nerve regeneration and to avoid mTOR inhibitors immediately after surgery. She experienced nephrotoxicity in spite of the multiple attempts to reduce the tacrolimus doses to the minimal therapeutic trough levels, and this was hampered by persistent allograft rejection. In particular, the diagnosis of antibody-mediated rejection required a therapeutic alternative to prevent rejection, rescue renal function, provide therapeutic immunosuppression, decrease complications and potentially decrease the development of donor-specific antibodies. After 30 months on belatacept, our patient tolerated well the initial monthly and currently the bimonthly doses, renal function has returned toward normal creatinine levels, and the skin biopsies after the initiation of belatacept have been free from rejection. Follow-up monitoring includes evaluation of function, laboratory exams, trough levels, and skin changes.

The mitigation of an emerging alloantibody response is worth highlighting and also is consistent with studies in kidney transplantation in nonhuman primates. Our recent NHP studies in VCA have demonstrated the absence of de novo donor-specific antibodies and the delay of rejection with a belatacept-based regimen (manuscript submitted). Three-year outcomes from the BENEFIT and BENEFIT-EXT studies performed in kidney transplant recipients have demonstrated lower overall frequencies for DSAs and de novo DSAs in belatacept-treated patients compared with cyclosporine-treated patients. Currently, our patient has not experienced rejection since the initiation of belatacept over 30 months ago. This case suggests that belatacept may be a reasonable maintenance immunosuppressive alternative for use in VCA, providing sufficient prophylaxis from rejection with a reduced side effect profile, the latter being particularly relevant for nonlife threatening conditions typically treated by VCA.

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Abbreviations

BENEFIT	belatacept evaluation of nephroprotection and efficacy as first-line immunosuppression trial
CMV	cytomegalovirus
CNIs	calcineurin inhibitors
CoB	costimulation blockade
EBV	epstein bar virus
FDI	first dorsal interossei
FFP	fresh frozen plasma
GFR	glomerular filtration rate
HDL	high-density lipoprotein
HLA	human leukocyte antigen
IMT	intimal medial thickness
IVIG	intravenous immunoglobulin
LDL	low density lipoprotein
MMF	mycophenolate mofetil
MRA	magnetic resonance angiography
NHP	nonhuman primate
PRA	panel reactive antibody
QD	one a day
RATG	rabbit antithymocyte globulin
VCA	vascularized composite allograft
WBC	white blood cell count

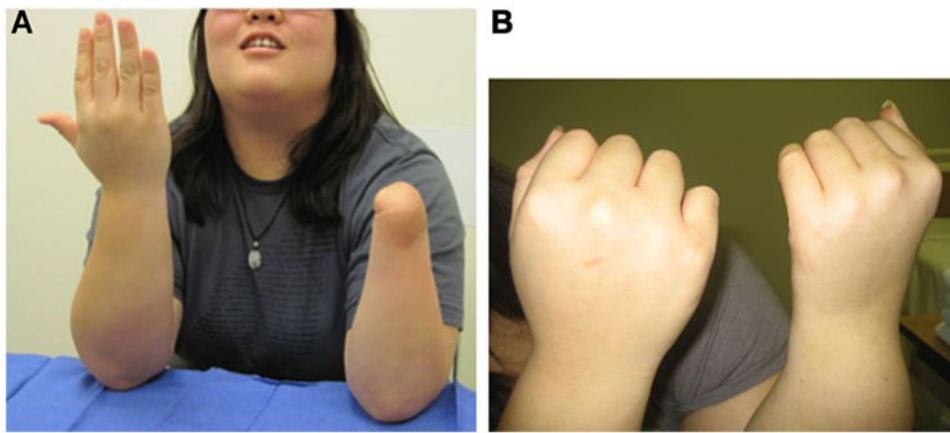


Figure 1. (A) and (B) Preoperative and postoperative status of the recipient. The left hand was amputated at the level of the wrist and the allograft was transplanted at the level of the distal forearm.

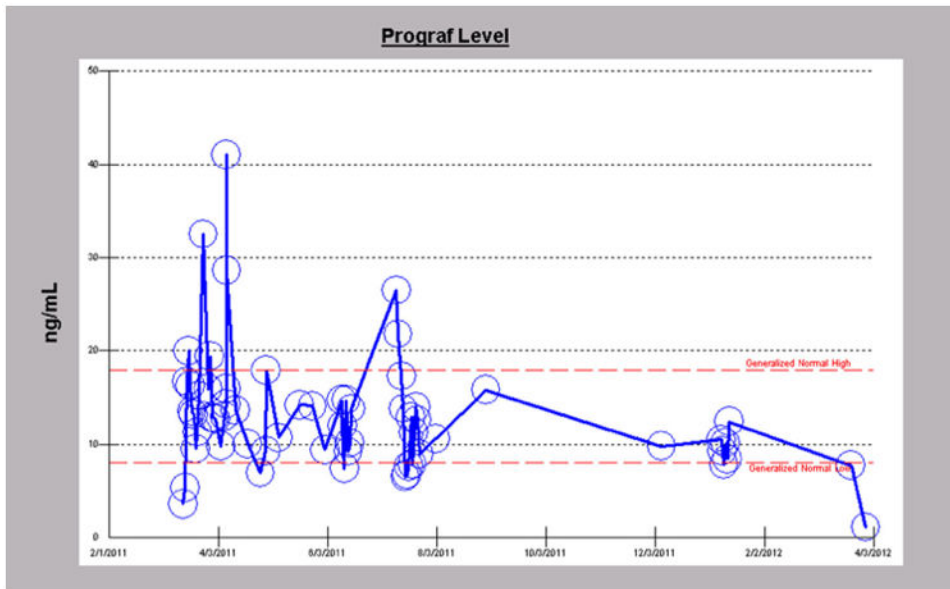


Figure 2. Tacrolimus levels after transplantation

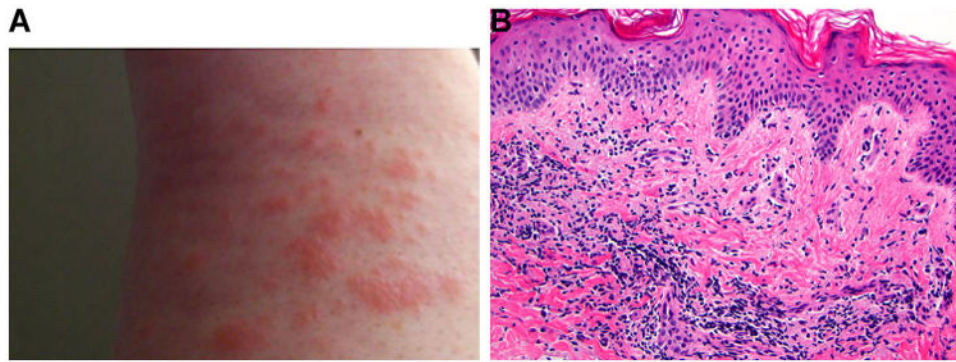


Figure 3. Visual and histologic findings during acute rejection

(A) Cutaneous eruption characterized by coalescent erythematous papules localized to the allograft. (B) VCA-Banff II rejection. Moderate perivascular and perieccrine lymphocytic infiltrate associated with epidermal spongiosis and exocystosis (Hematoxylin and Eosin 400 \times).

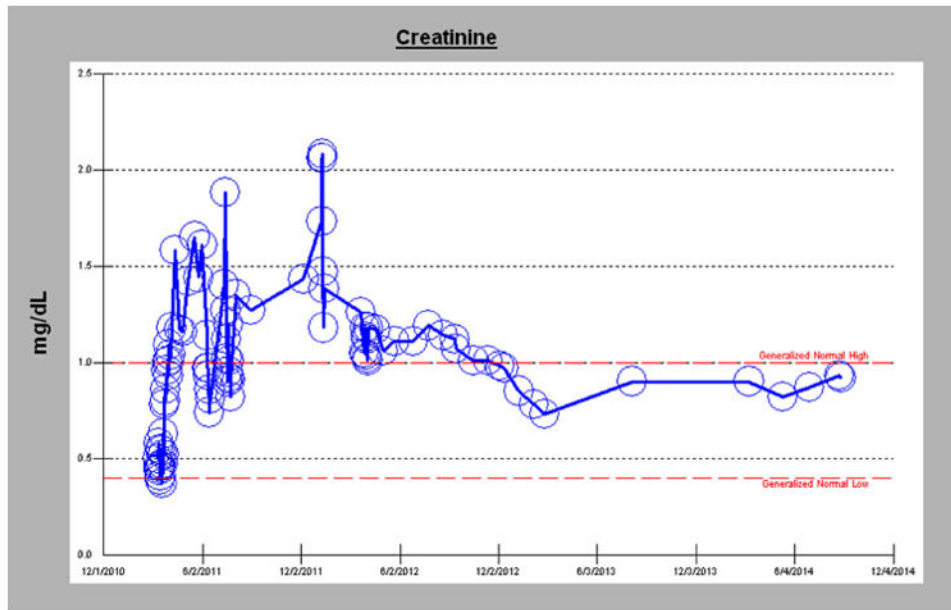


Figure 4. Creatinine levels after transplantation
The patient was initiated on tacrolimus on 3-2011 and converted to belatacept on 4-2012.



Figure 5.
(A) and (B) Bimanual activities that the patient initiated after transplant.

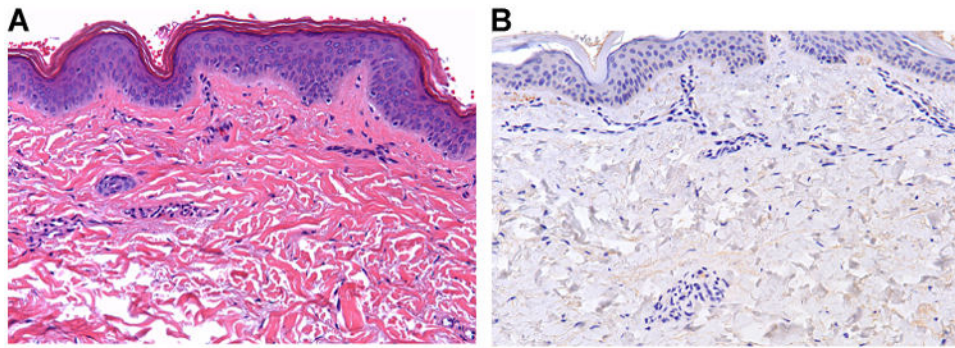


Figure 6. Histologic findings after 17 months on belatacept
(A) Banff 0 Hematoxylin and Eosin 400x], (B) C4d staining nonreactive.