DR. DAVID WOJCIECHOWSKI (Orcid ID : 0000-0001-5342-0277)

DR. JOSHUA YOUNG CYNMING YANG (Orcid ID : 0000-0003-2410-7817)

Article type : Original Article

Retrospective Evaluation of the Efficacy and Safety of Belatacept with Thymoglobulin Induction and Maintenance Everolimus: A Single Center Clinical Experience.

Wojciechowski D[1], Chandran S[2], Yang J[3], Sarwal M[3], Vincenti F[2*]

1: Division of Nephrology, Massachusetts General Hospital, Boston, MA
3: Division of Transplant Surgery, University of California San Francisco, San Francisco, CA
2: Division of Nephrology, University of California San Francisco, San Francisco, CA

*Corresponding author:
Flavio Vincenti, Flavio.Vincenti@ucsf.edu

Running title: Novel Regimen of Belatacept

Abbreviations:
cPRA: Calculated panel reactive antibody
CTOT: Clinical trials in organ transplantation
DGF: Delayed graft function
eGFR: Estimated glomerular filtration rate
ESRD: End stage renal disease
FDA: Food and Drug Administration
kSORT: Kidney solid organ response test
MDRD: Modification of diet in renal disease
MFI: Mean fluorescent intensity
mTORi: Mammalian target of rapamycin inhibitor
MMF: Mycophenolate mofetil
PCR: Polymerase chain reaction
PKD: Polycystic kidney disease
PTLD: Post transplant lymphoproliferative disorder
rATG: Rabbit anti-thymocyte globulin

Abstract

Belatacept use has been constrained by higher rates of acute rejection. We hypothesized that belatacept with low dose rATG and initial mycophenolate maintenance with conversion to everolimus at 1 month post-transplant ± corticosteroids would improve efficacy and maintain safety. Retrospective single center analysis of the first 44 low immunologic risk kidney transplant recipients treated with this regimen. The cohort was 59% male, mean age at transplant of 57 years. Diabetes was the most common cause of ESRD (39%). The mean 1 year eGFR was 61.4 (SD 18.4) mL/min/1.73 m^2. There were 5 acute cellular rejections (11.4%) and occurred in patients who had changed from everolimus to mycophenolate mofetil due to side effects. 32% developed BK viremia and 12% developed CMV viremia. There were no cases of PTLD. A novel belatacept regimen with rATG induction and maintenance everolimus demonstrated a low acute rejection rate and maintained an excellent 1-year eGFR.

Introduction

Belatacept was approved in June 2011 by the US Food and Drug Administration (FDA) for the prophylaxis of organ rejection in adult patients receiving a kidney transplant. Phase 3 clinical trials demonstrated a significantly higher 3-year estimated glomerular filtration rate (eGFR) in belatacept-treated patients compared to those maintained on cyclosporine. In the BENEFIT study the mean eGFR at 3 years was 65.8 mL/min/1.73 m^2 for the FDA approved belatacept regimen (less intensive; LI) versus 44.4 mL/min/1.73 m^2 for cyclosporine-treated patients ($P<0.0001$) (1). At 7 years of follow-up the belatacept LI treated patients had a mean eGFR of 72.1 mL/min/1.73 m^2 compared to 44.9 mL/min/1.73 m^2 for cyclosporine-treated patients (2). Additionally, the rates of death or graft loss with belatacept at 7 years were much lower at 12.8% versus 21.7% for cyclosporine (2). Despite these encouraging

results, the majority of new kidney transplant recipients in the US and at our center are discharged home on a calcineurin inhibitor.

One stumbling block to the more widespread adoption of belatacept is the demonstrated higher risk of early acute rejection. In BENEFIT the 1-year incidence of acute rejection was 17% and 7% for belatacept LI and cyclosporine-treated patients, respectively (1, 3). Furthermore, acute rejections were histologically more severe in the belatacept group, although rarely antibody mediated (1, 3). Patients in both groups were treated with basiliximab induction and were maintained on mycophenolate mofetil (MMF) and corticosteroids. The challenge faced by a transplant center is the task of optimizing a belatacept-based immunosuppression regimen to maintain excellent eGFR and improved long-term outcome while minimizing the risk of early acute rejection.

Preclinical data suggest that a mammalian target of rapamycin inhibitors (mTORi) might provide synergistic immunosuppression when coupled with costimulation blockade. In non-human primate models of renal and islet transplantation the combination of CTLA4-Ig and sirolimus successfully prevented rejection (4) and prolonged graft survival (5). Clinically, the data appear to be promising as well. In a Phase 2 study of renal transplant recipients, the combination of belatacept with rabbit anti-thymocyte globulin (rATG) induction (at 6 mg/kg total dose), maintenance sirolimus and early corticosteroid withdrawal provided excellent efficacy with a very low rate of acute rejection compared to patients treated with tacrolimus and MMF (6). A similar experience was reported in a pilot single center trial in which alemtuzumab was substituted for thymoglobulin as the induction agent (7).

Since the approval of belatacept, our center has sought to determine the optimal belatacept-based immunosuppression regimen for our patient population which would maximize both efficacy and safety. To this end, we devised a regimen of *de novo* belatacept

with low-dose rATG induction (low dose was chosen to achieve depletion, allow for earlier reconstitution and minimize toxicity and the risk of PTLD) (8), maintenance everolimus, with or without maintenance corticosteroids. In this report, we summarize our initial experience utilizing this novel regimen in our center as part of our immunosuppression protocols.

Methods

Patient Selection

This is a single-center, retrospective analysis of the first 44 patients with at least 1 year of post-transplant follow-up who received a novel *de novo* belatacept regimen from August 2012 to July 2015 at the University of California, San Francisco. Patients were eligible for the belatacept regimen if they met the following criteria: EBV IgG seropositive prior to transplant and low immunologic risk (cPRA ≤30%, no donor specific antibodies ≥500 mean fluorescent intensity [MFI], and negative crossmatch testing [by T and B cell flow or by virtual crossmatch]). Patients were excluded if they had a prior renal transplant, end-stage renal disease (ESRD) due to focal segmental glomerulosclerosis (FSGS), pediatric-en-bloc donor, concern for difficult intravenous access, difficulty traveling to an infusion center, and/or insurance coverage issues/high out of pocket patient cost for belatacept versus tacrolimus. Starting in 2012, this belatacept based regimen has been utilized as the standard of care protocol for all patients at our center receiving belatacept *de novo* post-transplant and therefore written informed consent was not required or obtained. The treatment team discussed potential immunosuppressive options with all patients; those who were clinically considered appropriate for belatacept therapy were treated with this

regimen. This study was approved by the institutional review board as a retrospective analysis.

Immunosuppression Protocols

All patients received corticosteroid induction with 500, 250, 125, 60, and 30 mg of IV methylprednisolone on days 0 to 4 post-transplant. Patients eligible for early corticosteroid withdrawal (ECSW) did not receive additional corticosteroids beyond day 4. Eligibility for early corticosteroid withdrawal was based on our center criteria: low immunologic risk (same as cited above), immediate graft function, non-African American race, and non-glomerulonephritis (GN) as the cause of ESRD. Ultimately, however, it was up to the treating physician to make the final decision regarding the use of maintenance corticosteroids. In patients on corticosteroid maintenance, prednisone was started on day 5 at 30 mg/day and tapered by 10 mg weekly to a final maintenance dose of 5 mg/day. Belatacept was dosed according to the LI dosing previously described (3, 9) and approved by the US FDA. However, there were differences in the timing of the first two doses: the first dose was given on postoperative day (POD) 1 and the second dose was given on POD 7 ± 3 in order to allow the second dose to be given preferentially as an outpatient. Patients received antibody induction with rATG (Thymoglobulin; Genzyme, Cambridge, MA) given as 3 mg/kg total dose over 2-3 days. This dose was chosen to maintain immediate post-transplant depletion but allow for earlier, more rapid reconstitution and to try to minimize the risk of infections and PTLD with this regimen (8). MMF was started on POD 0 administered at 2 g/day in divided doses and adjusted to maintain a white blood cell count >3.5 X 10^6/L; the dose was reduced for cytopenias or adverse drug reaction. The clinical protocol specified conversion from MMF to everolimus at 1-month post-transplant,

assuming stable graft function without significant proteinuria (urine protein: creatinine ratio <1 g/g) and no ongoing wound healing issues. Everolimus was started at 0.75 mg twice daily and the dose titrated to achieve a trough level of 3-8 ng/mL and adjusted to maintain a white blood cell count >3.5 X 10^6/L; the dose was reduced for adverse drug reaction. It should be noted that this was not a prospective trial but rather a clinical protocol therefore some variation on the initiation of everolimus (based on factors such as visit schedule, medication prior authorization and pharmacy pick up of medications by the patient) was expected.

Infection Prophylaxis Protocols

Patients received prophylaxis against *Pneumocystis jiroveci* pneumonia with sulfamethoxazole-trimethoprim (SMZ/TMP; 800/160) mg 1 tablet daily for 1 month followed by 1 tablet every Monday, Wednesday, and Friday for an additional 5 months. Patients received cytomegalovirus (CMV) prophylaxis with valganciclovir (900 mg) daily (dose adjusted for renal function by MDRD equation) for 3 months if both donor and recipient were CMV-naïve or the recipient was CMV-seropositive and for 6 months if the recipient was CMV-naïve and the donor was CMV-seropositive.

Laboratory Testing

Patients underwent routine laboratory monitoring that included serum creatinine, electrolytes, drug trough levels, and a complete blood count twice weekly for weeks 1-4, weekly for weeks 5-12, every 2 weeks for weeks 13-24, and monthly from weeks 25 to 52. BKV screening consisted of quantifying viral DNA in the plasma at 3, 6, 9, and 12 months after transplantation. BK viremia was considered positive at >500 copies/mL (the lower

limit of detection of our test). BK virus associated nephropathy (BKVAN) was diagnosed with a renal allograft biopsy confirming the presence of a positive SV-40 immunohistochemical stain. CMV screening was also performed by quantifying viral DNA in the plasma at months 3 and 6 after transplantation.

Indications for Kidney Transplant Biopsy

Kidney transplant biopsies were performed for surveillance at month 6 post-transplant and at any time for cause. Cause biopsies were performed in any patient with >25% increase in creatinine above baseline without an alternative explanation or for proteinuria >1 g/day.

Diagnosis and Treatment of Rejection

Rejection episodes were diagnosed with a kidney transplant biopsy. All biopsies were reviewed by a renal pathologist and scored according to the Banff 2005 classification (10). Banff 1a acute T cell rejections were treated with IV methylprednisolone 500 mg/day for 3 days followed by an oral corticosteroid taper. Banff 1b acute T cell rejections were treated with either the IV methylprednisolone pulse (as described above) or rATG at a total dose of 6 mg/kg given over 3-4 days at the discretion of the treating physician. Banff 2a and above acute T cell rejections were treated with rATG at the above dose. Patients diagnosed with acute rejection were switched from belatacept to tacrolimus at the discretion of the treating physician.

Immune Monitoring

A subset of patients underwent immune monitoring post-transplant via the kidney solid organ response test (kSORT). Details of this assay as well as results are included in the Supplemental Section.

Data Analysis

Outpatient and inpatient records were reviewed. Data obtained included demographics, transplant characteristics, laboratory results, and donor data. Data were analyzed using the GraphPad In Stat 3.10 software (GraphPad Software, Inc; La Jolla, CA). Descriptive statistics were generated. Continuous variables were analyzed using paired Student's t-test or Wilcoxon rank sum, as appropriate. Categorical variables were analyzed using the Chi-square or Fisher's exact test. The primary outcomes of interest were: 1-year eGFR (calculated by MDRD), 1-year acute rejection rate, and 1-year patient and graft survival. Additional outcomes evaluated included a 1-year assessment of safety parameters including PTLD and infectious complications.

Results

Study Population

44 patients received the *de novo* belatacept regimen and were included in this analysis. Baseline patient and transplant characteristics are summarized in Table 1. The majority of patients was male and 45.5% received a living donor kidney transplant. The patients were ethnically diverse with 25% being Hispanic, 11.4% African-American and 20.5% Asian. A total of 27.3% of patients experienced delayed graft function (defined as the need for renal replacement therapy in the first week post-transplant). Overall the patients were not highly sensitized with a mean cPRA was 6.1%.

Immunosuppression induction and maintenance exposure are listed in Table 2. Per clinical protocol, all patients received rATG induction. Most patients were maintained on

corticosteroids (81.8%) and 7 patients were converted to tacrolimus from belatacept (5 due to rejection, 1 due to borderline changes on a biopsy, and 1 due to poor IV access) at a mean of 127.5 days (range 45-344 days) after transplant. All patients underwent conversion from MMF to everolimus on average 42.9 days (median 30 days; range 21-211 days) after transplant. Seventeen patients (38.6%) were converted back to MMF due to an intolerance or adverse reaction to everolimus and this occurred on average 114.5 days (median 103 days; range 40-328 days) after transplant. In total 18 (40.9%) of the patients in our cohort discontinued or changed treatment regimen. The decision to convert back to MMF was made by the treating clinician. Documented reasons for everolimus discontinuation included: elevated blood pressure (n=2), pneumonitis (n=1), proteinuria (n=2), hyperglycemia (n=1), BK viremia (n=1), surgery for a small bowel obstruction (n=1), lower extremity pain and edema (n=1), non-healing diabetic foot ulcer (n=1), and oral aphthous ulcers (n=7).

Survival and Renal Function Data

There was one patient death with a functioning allograft (patient lived out of state and was admitted locally for a peri-rectal abscess with subsequent bowel ischemia and developed failure to thrive) yielding a 1-year patient survival of 97.7%. There was 100% death-censored graft survival at 1-year post-transplant. Renal function during the 1-year follow-up is listed in Table 3. At 1-year post-transplant the mean eGFR was 61.4 (SD 18.4) mL/min/1.73 m^2, up from 55.7 (SD 15.3) mL/min/1.73 m^2 at 1-month post-transplant. The mean eGFR at 1-year post-transplant for patients who remained on belatacept was 64.5 (SD 17.1) mL/min/1.73 m^2 versus 48.1 (SD 19) mL/min/1.73 m^2 for those who were converted from belatacept to tacrolimus (P = 0.03).

Renal Biopsy and Rejection Data

There were 12 for cause biopsies performed during the 1-year follow-up (Table 4). Two biopsies had no significant pathologic changes, 4 had borderline changes, and 1 had BK virus associated nephropathy (BKVAN). There were 2 Type 1a, 1 Type 1b, and 2 Type 2b rejections. There were no acute antibody mediated rejections. All acute cellular rejection events occurred in patients who had been switched back to MMF from everolimus. On average the conversion from everolimus back to MMF in patients with acute rejection occurred 87.7 days (range 40 to 153 days) post-transplant while the rejection event occurred on average 148.2 days (range 44-256 days) post-transplant. The immunosuppression regimen for all 5 patients with acute rejection at the time of the biopsy is summarized in Table 5 as well at the timing of rejection in relation to the start day of everolimus and conversion back to MMF. The acute rejection rate, therefore, was 11.3% with 40% of the events occurring in patients in whom corticosteroids were withdrawn early. A total of 30 (68.2%) patients underwent a 6-month protocol biopsy with only one subclinical rejection (Banff Type 1a) identified. This patient was receiving belatacept and everolimus with early corticosteroid withdrawal and had a stable serum creatinine at the time of biopsy. The immunosuppression regimen for the remaining patients at the time of the 6-month protocol biopsy was as follows: belatacept/everolimus/ECSW 1; belatacept/MMF/ECSW 4; belatacept/everolimus/steroid maintenance 19; belatacept/MMF/steroid maintenance 3; tacrolimus/everolimus/steroid maintenance 1; tacrolimus/MMF/ECSW 1. Not all patients underwent a protocol biopsy due to various reasons including the following: use of warfarin/anti-platelet therapy 7; prior for cause biopsy close to the 6-month time point 2; overlying bowel with no biopsy window 2; patient

lived out of state 1; procedure aborted due to severe patient anxiety 1; biopsy performed but inadequate sample obtained 1.

Safety Data

There were no cases of post-transplant lymphoproliferative disorder (PTLD). Fourteen patients (31.8%) developed BK viremia; 4 (9.1%) and 1 (2.3%) patient developed CMV viremia and CMV disease (colitis), respectively. There were 4 (9.1%) patients with urinary tract infections.

Discussion

In this initial experience with a novel *de novo* belatacept regimen we show that the combination of belatacept and lymphocyte depleting induction therapy is safe and well tolerated with an acceptable profile of infections and without any cases of PTLD. Further, with the addition of maintenance everolimus, this regimen demonstrated a low acute rejection rate, comparable to that seen in patients receiving calcineurin inhibitor based regimens. Graft function remained excellent with eGFR similar to that seen at 1-year in the BENEFIT study; although it should be pointed out that in making this comparison we are evaluating two different regimens as well as data from a prospective, randomized trial to a retrospective analysis.

The 1-year acute rejection rate of 11.3% seen in our belatacept cohort is numerically lower than that seen in belatacept LI patients in BENEFIT at 17% (1, 3), and similar to the 4% rate seen in the Phase 2 trial by Ferguson *et al* which combined belatacept with rATG induction and maintenance sirolimus in 26 renal transplant recipients (6). Drug dosing and exposure

differences between the cohorts may account for the difference in the incidence of acute rejection. Ferguson *et al* utilized a higher induction dose of rATG (6 mg/kg) compared to that used (3mg/kg) in our cohort. In their cohort, 12 patients (46%) discontinued or switched treatment in the belatacept and sirolimus group, with most switches occurring within the first 60-90 days and none of the conversions being performed in response to acute rejection (although it is noted that one was due to graft dysfunction and one due to graft loss). In our cohort 8 patients (18.2% of the total cohort) were converted from belatacept to tacrolimus with 7 of those conversions due to acute rejection or borderline changes on a biopsy. Half of the conversions occurred at >90 days post-transplant. It is possible that the earlier time point of conversion from belatacept to tacrolimus in the belatacept-sirolimus group of the Ferguson study contributed to a slightly lower subsequent acute rejection rate. This is plausible given that 82% of acute rejections seen in the belatacept arm of the BENEFIT study occurred within the first 90 days (1, 3). Finally, in our cohort everolimus was added on average 43 days after transplant to avoid post-operative wound complications whereas sirolimus was started on POD 1 in the cohort of Ferguson *et al*. The mean everolimus levels in our cohort were 5.2 ng/ml and 5.7 ng/ml at 3 and 12 months respectively compared to sirolimus levels of 17.7 ng/ml and 9 ng/ml at 2 weeks and 12 months respectively (3-month data not available) in the cohort of Ferguson *et al*. It is tempting to speculate that the potential synergy between belatacept and an mTORi is best harnessed with a higher dose of the mTOR inhibitor and a maximal period of overlap between the two drugs starting within a week post-transplant.

It is important to note that 38.6% of patients in our cohort did not tolerate everolimus and required conversion back to MMF. This is very similar to the sirolimus intolerance rate of 38.5% seen in the cohort of Ferguson *et al* (6). This is also comparable to the rate of discontinuation of everolimus in a large multicenter study of reduced dose cyclosporine with two different fixed doses of everolimus in which up to 34.1% of subjects discontinued everolimus (11). Additionally, in the study by Ferguson *et al* a total of 46% of their patients randomized to belatacept and sirolimus either discontinued or changed treatment, similar to the rate of 40.9% seen in our cohort.

While experiencing a lower acute rejection rate compared to BENEFIT our patients also maintained good graft function. In BENEFIT the belatacept LI patients had a mean eGFR of 63.4 (SD 27.7) mL/min/1.73 m^2 at 1-year (3) which is in line with what we found in our cohort, a mean eGFR of 61.4 (SD 18.4) mL/min/1.73 m^2. It remains to be seen whether the belatacept-treated patients in our cohort will experience a positive eGFR slope as seen in BENEFIT.

Our cohort demonstrated a BK viremia incidence at 1 year post-transplant of 31.8%. Although seemingly higher than what has been previously reported in the literature it is only slightly higher than an incidence of 25% reported by our group in a previous report (12). However, we believe the impact of belatacept on the risk of BK viremia merits further investigation and that work is ongoing at this time.

The major limitations of our analysis include its retrospective nature, relatively small numbers, lack of a control group to compare outcome data and the heterogeneity in overall immunosuppression with regard to maintenance corticosteroids and the initiation of everolimus. As a clinical protocol (and not a prospective study) some variability is not

unexpected and was noted with the initiation of everolimus. We are a step closer towards reaching an optimal belatacept regimen but there remain multiple challenges to be overcome. While patients who remained on belatacept and everolimus in our cohort had excellent outcomes overall, nearly 1 in 4 patients had to stay on or switch back to MMF. Although this rate of everolimus discontinuation is comparable to that seen in other studies, it may be of particular concern when everolimus is used as part of a belatacept containing regimen, given that nearly all rejections occurred in patients who were not on everolimus and that 29% of the patients who stayed on or switched back to MMF developed an acute rejection subsequently.

The specific basis of the synergy between belatacept and mTOR inhibitors is unclear although the mechanism could be related to the expansion of regulatory T cells. While belatacept has an adverse effect on the survival and fitness of Tregs, mTOR inhibitors may mitigate this effect thought more direct effects on Tregs. Of note, two of the five rejections occurred in patients in whom steroids were withdrawn, and these results raises concerns about the safety of steroid withdrawal in belatacept containing regimen. Both CTOT -10 (NCT01436305) and CTOT-16 (NCT01856257), which utilized steroid withdrawal in conjunction with belatacept in kidney transplant recipients, were associated with high rejection rates resulting in study termination. A similar experience was seen by Adams *et al* (13) when they attempted steroid withdrawal. Our current *de novo* belatacept regimen now incorporates the maintenance of low dose steroids in all recipients of this regimen.

The risk of rejection with this regimen could potentially be mitigated further by the careful selection of patients with a view to their future tolerance of everolimus, closer monitoring of their immune status at points of drug conversion, and by avoiding steroid withdrawal in

these patients. However, despite these limitations, we believe that the data provided by our analysis add to the body of knowledge examining the best utilization of belatacept in kidney transplant recipients. A prospective randomized trial was underway comparing *de novo* belatacept with everolimus and early corticosteroid withdrawal versus tacrolimus/MMF and early corticosteroid withdrawal in combination with rATG induction in both groups (NCT02137239) but was stopped prematurely by the sponsor. Another study (NCT01729494) comparing early corticosteroid withdrawal in three groups of patients- those receiving belatacept and MMF with either alemtuzumab or rATG induction and those receiving tacrolimus and MMF with rATG induction- has completed enrollment. Epsinosa *et al* have identified a pre-transplant population of CD57+PD1− CD4+ cells that correlates with the risk of rejection in belatacept treated patients (14). The development of a screening tool which incorporates these and other markers will be instrumental in the wider application and safe utilization of belatacept containing regimens.

In summary, we describe a novel belatacept regimen which uses low dose rATG induction to delete primed T cells and favor Treg expansion, and incorporates everolimus into the maintenance regimen to harness the synergy with belatacept. This regimen, utilized as part of a real-world experience in a large volume transplant center, demonstrated a low acute rejection rate and maintained an excellent 1-year eGFR, without an adverse safety profile of PTLD or infections.

Acknowledgments

This work was supported by an investigator initiated grant from Bristol-Myers Squibb (IM103-353).

Disclosure

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Drs. Wojciechowski, Chandran and Vincenti have received research funding from Bristol-Myers Squibb and Novartis.

Tables

Table 1: Baseline patient and transplant characteristics

De Novo Belatacept, n	44
Race/Ethnicity, n (%)	
Caucasian	30 (68.2)
Not Hispanic	19 (43.2)
Hispanic	11 (25)
African American	5 (11.4)
Asian	9 (20.5)
Male Gender, n (%)	26 (59)
Age at Transplant, years (SD)	56.9 (12.3)
Donor Type, n (%)	
Living	20 (45.5)
Standard deceased	18 (40.9)
ECD/DCD	6 (13.6)
KDPI, mean (SD)	46.6 (24.9; n=24)
Etiology of ESRD, n (%)	
DM	17 (38.6)
HTN	6 (13.6)
PKD	10 (22.7)
GN	5 (11.4)
Other	6 (13.6)
cPRA, mean (SD)	6.1 (13.6)
HLA mismatches, mean (SD)	4.1 (1.4)
DGF, n (%)	12 (27.3)
Ureteral stent placed at transplant, n (%)	4 (9.1)

ECD: expanded criteria donor; DCD: donation after cardiac death; KDPI: kidney donor profile index; DM: diabetes mellitus; HTN: hypertension; PKD: polycystic kidney disease; GN: glomerulonephritis; cPRA: calculated panel reactive antibody; HLA: human leukocyte antigen; DGF: delayed graft function.

Table 2: Immunosuppression exposure

De Novo Belatacept, n	44
Induction agent, n (%)	
rATG	44 (100)
Corticosteroid regimen	
Maintenance, n (%)	36 (81.8)
Early withdrawal, n (%)	8 (18.2)
Tacrolimus trough mg/dL, mean (SD)	
Month 3	10.7 (0.2; n=3)
Month 6	6.7 (3.3; n=5)
Month 9	7.4 (3.9; n=7)
Month 12	8.3 (6.4; n=7)
MMF dose mg/ day, mean (SD)	
Month 3	1666.7 (556.4; n=6)
Month 6	1772.73 (343.8; n=13)
Month 9	1458.3 (541.8; n=14)
Month 12	1333.3 (556.3; n=17)
Everolimus trough mg/dL, mean (SD)	
Month 3	5.2 (2.6; n=38)
Month 6	5.3 (2.5; n=31)
Month 9	5.8 (1.7; n=29)
Month 12	5.7 (2.5; n=26)

rATG, rabbit antithymocyte globulin; SD, standard deviation; MMF, mycophenolate mofetil.

Table 3: Renal function

eGFR mL/min/1.73 m^2, mean (SD)*	
Month 1	55.7 (15.3)
Month 3	65 (16.3)
Month 6	60.7 (14.9)
Month 9	61.3 (18.9; n=43)
Month 12	61.4 (18.4; n=43)

*By MDRD equation.

eGFR, estimated glomerular filtration rate; SD, standard deviation; MDRD: modification of diet in renal disease.

Table 4: For cause renal allograft biopsy results by Banff classification

Cause Biopsy, n	12
Negative for rejection, n	2
Borderline change, n	4
Acute cellular rejection, n	5
Type 1a	2
Type 1b	1
Type 2b	2
BK Virus Associated Nephropathy, n	1

Table 5: Immunosuppression regimens and timing of immunosuppression changes for patients with acute cellular rejection

Type of Rejection	Immunosuppression	POD of conversion to everolimus; from everolimus to MMF; rejection event
Type 1a	belatacept/MMF/steroid maintenance	30; 153; 229
Type 1a	belatacept/MMF/ECSW	40; 96; 119
Type 1b	belatacept/MMF/ECSW	30; 40; 44
Type 2b	belatacept/MMF/steroid maintenance	34; 59; 93
Type 2b	belatacept/MMF/steroid maintenance	28; 103; 256

POD: post-operative day; ECSW: early corticosteroid withdrawal; MMF: mycophenolate mofetil

References

1. Vincenti F, Larsen CP, Alberu J, Bresnahan B, Garcia VD, Kothari J, et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel-group study in adult kidney transplant recipients. Am J Transplant. 2012;12(1):210-7.
2. Vincenti F, Rostaing L, Grinyo J, Rice K, Steinberg S, Gaite L, et al. Belatacept and Long-Term Outcomes in Kidney Transplantation. N Engl J Med. 2016;374(4):333-43.
3. Vincenti F, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P, et al. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). Am J Transplant. 2010;10(3):535-46.
4. Lo DJ, Anderson DJ, Weaver TA, Leopardi F, Song M, Farris AB, et al. Belatacept and sirolimus prolong nonhuman primate renal allograft survival without a requirement for memory T cell depletion. Am J Transplant. 2013;13(2):320-8.
5. Lowe MC, Badell IR, Turner AP, Thompson PW, Leopardi FV, Strobert EA, et al. Belatacept and sirolimus prolong nonhuman primate islet allograft survival: adverse consequences of concomitant alefacept therapy. Am J Transplant. 2013;13(2):312-9.
6. Ferguson R, Grinyo J, Vincenti F, Kaufman DB, Woodle ES, Marder BA, et al. Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. Am J Transplant. 2011;11(1):66-76.
7. Kirk AD, Guasch A, Xu H, Cheeseman J, Mead SI, Ghali A, et al. Renal transplantation using belatacept without maintenance steroids or calcineurin inhibitors. Am J Transplant. 2014;14(5):1142-51.
8. Kho MM, Bouvy AP, Cadogan M, Kraaijeveld R, Baan CC, Weimar W. The effect of low and ultra-low dosages Thymoglobulin on peripheral T, B and NK cells in kidney transplant recipients. Transplant immunology. 2012;26(4):186-90.
9. Durrbach A, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J, et al. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT study). Am J Transplant. 2010;10(3):547-57.
10. Solez K, Colvin RB, Racusen LC, Sis B, Halloran PF, Birk PE, et al. Banff '05 Meeting Report: differential diagnosis of chronic allograft injury and elimination of chronic allograft nephropathy ('CAN'). Am J Transplant. 2007;7(3):518-26.
11. Tedesco Silva H, Jr., Cibrik D, Johnston T, Lackova E, Mange K, Panis C, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. Am J Transplant. 2010;10(6):1401-13.

12. Wojciechowski D, Chanda R, Chandran S, Lee B, Webber A, Macaraig M, et al. Ciprofloxacin prophylaxis in kidney transplant recipients reduces BK virus infection at 3 months but not at 1 year. Transplantation. 2012;94(11):1117-23.
13. Adams A GC, Chami A, Harler M, Pastan S, Kirk A, Pearson T, Larsen C., editor Belatacept Post-Approval Implementation: A Large Single Center Experience. American Transplant Congress; 2013.
14. Espinosa J, Herr F, Tharp G, Bosinger S, Song M, Farris AB, 3rd, et al. CD57(+) CD4 T Cells Underlie Belatacept-Resistant Allograft Rejection. Am J Transplant. 2016;16(4):1102-12.