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Comparison of Utilization and Clinical Outcomes for Belatacept- and Tacrolimus- Based Immunosuppression in Renal Transplant Recipients

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Running Title:

Comparison of Belatacept and Tacrolimus

Abbreviations:

aHR	Adjusted Hazard Ratio
BMI	Body Mass Index
BENEFIT	Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial
BENEFIT-EXT	Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial-EXTended criteria donors
BPAR	Biopsy Proven Acute Rejection
CI	Confidence Interval
CNI	Calcineurin Inhibitor
EBV	Epstein-Barr Virus
ECD	Extended Criteria Donor
eGFR	Estimated Glomerular Filtration Rate
FDA	Federal Drug Administration
cPRA	Calculated Panel Reactive Antibody
DM	Diabetes Mellitus
ESRD	End Stage Renal Disease

HLA	Human Leukocyte Antigen
KTR	Kidney Transplant Recipients
LD	Lymphocyte Depleting
MDRD	Modification of Diet in Renal Disease
NODAT	New Onset Diabetes after Transplantation
OPTN	Organ Procurement and Transplantation Network
PTLD	Post-Transplant Lymphoproliferative Disease
SCD	Standard Criteria Donors
SRTR	Scientific Registry of Transplant Recipients
SD	Standard Deviation

Abstract

The performance of belatacept in a real clinical setting has not been reported. A retrospective cohort study was conducted using registry data comparing one-year clinical outcomes between belatacept- and tacrolimus-treated adult kidney transplant recipients (KTR) from 6.1.2011 through 12.1.2014. Of 50 244 total patients, 417 received belatacept+tacrolimus, 458 received belatacept alone, and 49 369 received tacrolimus alone at discharge. In the overall study cohort, belatacept alone was associated with a higher risk for one-year acute rejection, with highest rates associated with non-lymphocyte depleting (LD) induction (aHR: 2.65; 95%CI: 1.90-3.70, P<.0001). There was no significant difference in rejection rates between belatacept+tacrolimus and tacrolimus alone. In KTR meeting inclusion criteria for the BENEFIT-EXT trial, one-year kidney function was higher with

belatacept+tacrolimus and belatacept alone versus tacrolimus alone groups (mean eGFR: 65.6 vs 60.4 vs 54.3 ml/min/1.73M^2, respectively, P<.001). The incidence of new onset diabetes after transplantation was significantly lower with belatacept+tacrolimus and belatacept alone versus tacrolimus alone (1.7% vs 2.2% vs 3.8%, respectively, P=.01). Despite improved graft function and metabolic complications with belatacept alone, it may be advisable to add short-term tacrolimus the first year post-transplant and consider LD induction in high rejection risk patients, as the risk to benefit ratio allows.

Introduction

Standard maintenance immunosuppression regimens following kidney transplantation typically include a calcineurin inhibitor (CNI), either cyclosporine or tacrolimus, combined with mycophenolate mofetil and corticosteroids (1). CNI use over the past few decades has been associated with a reduction in the incidence of acute rejection (AR) and improvement in short-term allograft survival (2). However, while some clear gains have been made, improvements in long-term allograft survival have not been commensurate with those in the short-term (3). CNI nephrotoxicity has long been considered to be one of the numerous factors that contribute to long-term damage to transplant kidneys, although recent evidence implicates alloimmunity as a major determinant of late kidney allograft loss (4-6). In general, CNI withdrawal or avoidance strategies have not been very successful at preserving long-term graft function, and to date the CNIs still remain as the cornerstone of immunosuppression for renal transplant patients (7). However, in addition to being nephrotoxic, CNIs are significantly correlated with higher cardiometabolic complications, including post-transplant hypertension, diabetes, and hyperlipidemia (1). A long-term goal of the transplant community is to find an alternative immunosuppressive agent in lieu of CNIs that is not inherently nephrotoxic, protects adequately against alloimmunity, and does not increase cardiometabolic complications.

Belatacept (Nulojix®; Bristol-Myers Squibb, Princeton, NJ) is a fusion receptor protein (CTLA4-Ig) developed as a selective co-stimulation blocker, with two amino acid substitutions in the CTLA4 binding domain that dramatically increase binding to CD80/CD86, resulting in effective inhibition of T-cell activation (8). The first phase III clinical trial, Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) was a one-year, randomized, active-controlled, multi-center trial conducted at 100 centers worldwide that targeted adult recipients of kidneys from living or standard criteria deceased donors (SCD) (9). The second phase III clinical trial, Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial-EXTended criteria donors (BENEFIT-EXT), targeted adult recipients of extended criteria deceased donor (ECD) kidneys (10). Both trials showed non-inferior composite (patient death or graft loss) outcome and improved renal function and cardiovascular outcomes at one year in the belatacept-treated compared with the cyclosporine-treated patients. Belatacept patients experienced a higher yet non-inferior incidence of acute rejection episodes in the BENEFIT trial in the lower intensity FDA-approved dosage regimen compared with the cyclosporine-treated patients, whereas in the BENEFIT-EXT trial, the incidence of acute rejection was similar across groups. At seven years after transplantation in the BENEFIT trial, patient and graft survival and the mean eGFR were significantly higher with belatacept than with cyclosporine (11).

Although FDA approval for the drug was received in June 2011, the experience regarding the utilization and outcomes of belatacept in a real clinical setting, where over 90% of renal transplant recipients in the U.S receive a tacrolimus-based regimen, have not yet been reported (2). In this study, the utilization pattern of belatacept in the U.S., as well as efficacy and safety outcomes associated with its use, were examined.

Materials and Methods

Study Population

A retrospective observational study based on registry data from the Scientific Registry of Transplant Recipients (SRTR) and approved by the University of Florida Institutional Review Board (Protocol #201400666) was conducted to compare utilization patterns and clinical outcomes between belatacept- and tacrolimus-treated kidney transplant recipients (KTR). SRTR data, including data on all donors, wait-listed candidates, and transplant recipients in the U.S, was collected by the members of the Organ Procurement and Transplantation Network (OPTN). The activities of the OPTN and SRTR contractors are administered by the Health Resources and Services Administration of the U.S. Department of Health and Human Services. The study included solitary KTR 18 years or older who received belatacept+tacrolimus-, belatacept- (without CNI, termed belatacept alone) or tacrolimus- (without belatacept, termed tacrolimus alone) based regimens at hospital discharge following transplant surgery after June 1st, 2011 and followed up through December 1st, 2014. Recipients were excluded if they received other organ transplants or used cyclosporine as a maintenance immunosuppressant drug at hospital discharge.

Outcomes

Patients were followed from the date of transplantation until death, graft loss (reported in SRTR as return to dialysis or re-transplantation), loss to follow-up, or 1 year after the transplant date, whichever came first. The primary outcomes for the study included: one-year composite patient death or graft loss and one-year incidence of biopsy-proven acute rejection (BPAR). The secondary outcomes included mean estimated glomerular filtration rate (eGFR) at 1 year using the modification of diet in renal disease (MDRD) equation (mL/min/1.73m^2) (12, 13), the one-year incidence of new-onset diabetes after transplantation (NODAT), and the one-year incidence of post-transplant

lymphoproliferative disease (PTLD) and other new-onset malignancy. Primary and secondary outcomes within 1 year were compared between belatacept+tacrolimus-, belatacept alone- and tacrolimus alone-treated patients. Further analyses were conducted in the subgroups to investigate the association of drug regimens and outcomes in specific patient populations.

Covariates

Recipient demographic and clinical characteristics, as well as donor characteristics, were examined for the belatacept- and tacrolimus-treated groups. Recipient covariates in this study included: age, race (black versus others), gender, BMI (obese defined as BMI $\geq$30 kg/m^2 versus non-obese, BMI<30 kg/m^2), pre-transplant cardiovascular disease, previous history of malignancy, previous kidney transplant, steroid use at hospital discharge, mycophenolate use at hospital discharge, cause of end stage renal disease (hypertension, diabetes, glomerulonephritis, polycystic kidney disease, and other), recipient panel reactive antibody (PRA), pre-transplant dialysis duration (>2 years, 0-2 years versus none), HLA mismatch (>3 versus $\leq$3), induction with lymphocyte-depleting (LD) agents (antithymocyte globulin or alemtuzumab), recipient insurance (private versus others), and recipient Epstein-Barr virus (EBV) serostatus (positive or negative). Donor characteristics were: age, gender, race, and graft types (living donor, SCD, or ECD).

Center Effect

Belatacept use was not uniform in U.S. transplant centers. Only 25% of U.S. transplant centers had begun to use belatacept prior to December 01, 2014. Fifty seven percent of KTR who received belatacept by that date were transplanted at just one of the sixty U.S. centers using the drug, which was named “major belatacept center”. Based on SRTR discharge immunosuppression records, seventy five percent of the recipients who received belatacept at the major belatacept

center were treated with a combined regimen of belatacept+tacrolimus. The other 59 transplant centers in this study, whose rate of belatacept use ranged from 0.1% to 15.8%, were grouped together and named "other belatacept centers". The risks associated with the major and other belatacept center types was defined as a co-variate "center effect" for the purpose of adjustments in the multivariable models.

Subgroup Analysis

Subgroup analyses were performed to investigate the associations of different induction drugs (LD or non-LD) as part of each immunosuppression regimen with the clinical outcomes related to belatacept use. Multivariate analyses were performed for the two primary outcomes in the entire study cohort, as well as for the two different induction groups. To compare the current study results with those from the two major belatacept clinical trials, BENEFIT and BENEFIT-EXT, the primary clinical outcomes were also analyzed in patients who met the same inclusion and had none of the exclusion criteria specified in these trials. Specifically, those recipients meeting criteria for the BENEFIT trial (living donor or SCD, with cold ischemia time < 24h and PRA < 50% for first transplants and < 30% for re-transplants) were designated as BENEFIT-eligible recipients, while those recipients meeting criteria for the BENEFIT-EXT trial (donors ≥60 years old; or donors ≥50 years old who had at least two other risk factors of hypertension, death from cerebrovascular accident, or serum creatinine >1.5mg/dL; or cold ischemia time of ≥24 hours; or donation after cardiovascular death) were designated as BENEFIT-EXT-eligible recipients. High PRA KTR, defined as first-time transplants with a PRA ≥50% or re-transplants with a PRA ≥30% (exclusion criteria for both BENEFIT and BENEFIT-EXT trials) were also investigated.

Statistical Analysis

Categorical variables were compared between the comparison groups using chi-square tests, whereas continuous variables were compared using student t-tests for two-group comparison and F test for more than two-group comparison. Multivariate Cox proportional hazards model was used to assess the hazard ratio for the first occurrence of patient death or graft loss or BPAR within the first post-transplant year comparing three different regimens. The assumption of proportional hazards underlying the Cox model was tested and confirmed by visually inspecting the complementary log-log survival plots for the primary explanatory variables and by examining the Schoenfeld residual plots. To fit the multivariate model, a univariate analysis was first conducted with the major exposure variable and then with each covariate added one at a time to examine the change of the estimate of the major exposure variable. The covariates that modified the estimate of the major exposure variable over 3% were kept in the final multivariate model. All analyses were conducted using SAS 9.4 (Cary, NC). The significance level was set at $P<.05$, unless multiple comparisons were conducted.

Results

Patient characteristics

A total of 50 244 adult recipients underwent solitary kidney transplantation from June 1, 2011 through December 1, 2014. Based on immunosuppression reported at the time of discharge, 875 KTR received a belatacept regimen (417 concomitantly with tacrolimus and 458 on belatacept alone). A total of 49 369 KTR received tacrolimus but not belatacept (tacrolimus alone). At 12 months post-transplant, 54%, 57%, and 66% of patients in the belatacept+tacrolimus, belatacept alone, and tacrolimus alone groups, respectively, had reported post-transplant immunosuppressant information. Only 29%, 44%, and 63% of

patients in these groups maintained the discharge drug regimens at one-year follow up, respectively. Out of 417 belatacept+tacrolimus-treated patients at 1 year, 123 remained on belatacept+tacrolimus at 12 months, 71 were treated with belatacept alone, 26 were treated with tacrolimus alone, and 4 were switched to other immunosuppressants. None of belatacept+tacrolimus-treated patients in "other belatacept centers" maintained the discharge drug regimen at 12 months.

The demographic and clinical characteristics of the belatacept+tacrolimus-, belatacept alone-, and tacrolimus alone-treated patients are compared in Table 1. Most of the P values for the comparisons between cohorts appear significant due to the large sample size. However, only the following factors achieved a clinically meaningful difference of >10% between cohorts: induction drug use, EBV seropositivity, recipient PRA, recipient race, steroid use and transplant center. Patients who received a belatacept+tacrolimus regimen were more likely than belatacept-alone and tacrolimus-alone patients to have received a transplant at the major belatacept center (90% vs 28% vs 0.43%, P<.0001, respectively). Compared to belatacept alone-treated patients, belatacept+tacrolimus-treated patients were also more likely to be sensitized (PRA higher than 20%: 37% vs 21%, respectively; P<.0001), be African American (49% vs 23%, P<.0001), and be retransplants (10% vs 5%, P=.0025), while less likely to have received LD induction drugs (7% vs 51%, P<.0001). Thus, aside from being discharged more often on steroids (92% vs 77%, P<.0001), the patients who received the belatacept+tacrolimus regimen had overall more baseline factors considered to increase the risk for acute rejection.

Patient/graft survival

All patient and graft survival outcomes data are listed in Table 2. The rates of one-year patient death, death with functioning graft, death-censored graft loss, and composite patient death or graft loss in the two belatacept (belatacept+tacrolimus and belatacept alone) regimens were not significantly different than those of the tacrolimus alone group.

Acute rejection

Figure 1a compares the unadjusted one-year BPAR rates of the overall study population, BENEFIT-eligible recipients, and BENEFIT-EXT-eligible recipients. The rates of one-year BPAR were numerically similar between belatacept+tacrolimus- and belatacept alone-treated KTR in the overall study population (16.8% vs 18.8%, P=.44), BENEFIT-eligible patients (15.7% vs 16.7%, P=.75), and BENEFIT-EXT-eligible patients (17.1% vs 19.1%, P=.71). However, these rejection rates (in the belatacept+tacrolimus- and belatacept alone-treated KTR) were significantly higher than those in the tacrolimus alone-treated KTR across the three comparison groups (6.5% in all patients, 6.0% in BENEFIT-eligible, 6.6% in BENEFIT-EXT-eligible patients).

Figure 1b compares the one-year BPAR rates between treatment groups under LD and non-LD induction regimens. The use of LD induction drugs was associated with lower one-year BPAR rates in the KTR who received belatacept-alone (14.6% vs 23.1%, P=.02), with no significant difference observed in belatacept+tacrolimus recipients (20.7% vs 16.5%, P=.56). Subgroup analysis in belatacept-alone treated KTR meeting BENEFIT-EXT criteria demonstrated a high rejection rate in those receiving non-LD induction (27.1%) compared to those

receiving LD induction (11.9%, P=.03). The lowest rejection rates were observed in the tacrolimus-alone group with either induction agent (6.2% in LD induction, and 7.1% in non-LD induction).

High PRA recipients, who were excluded from the BENEFIT and BENEFIT-EXT clinical trials, experienced more one-year BPAR in the two belatacept groups than in the tacrolimus alone group (19.7% vs 36.4% vs 8.3% for belatacept+tacrolimus, belatacept alone, and tacrolimus alone, respectively, P<.0001). The highest rate of one-year BPAR occurred in the belatacept alone-treated high PRA patients who received non-LD induction (43%).

Table 3 contains the adjusted hazard ratios for BPAR within one year of transplantation with belatacept+tacrolimus vs tacrolimus alone treatments, ~~and~~ belatacept alone vs tacrolimus alone treatments, and belatacept+tacrolimus vs belatacept alone treatments. Compared with tacrolimus alone, a significantly increased risk of BPAR associated with belatacept alone use within the first year was identified in the overall study cohort (aHR: 2.36; 95%CI: 1.82-3.05, P<.0001), BENEFIT-eligible recipients (aHR: 2.51, 95%CI: 1.79-3.52, P<.0001), BENEFIT-EXT-eligible recipients (aHR: 1.74, 95%CI: 1.06-2.85, P<.03), recipients who received LD induction (aHR: 1.86; 95%CI: 1.20-2.90, P=.006), and recipients who received non-LD induction (aHR: 2.65; 95%CI: 1.90-3.70, P<.0001). Compared with tacrolimus alone, belatacept+tacrolimus treatment was not significantly associated with an increased risk of BPAR within 1 year in the overall study cohort or subgroup analyses, although the BPAR risk was suggestively higher in recipients who received LD induction **(**aHR: 2.35; 95%CI: 0.94 – 5.90, P=.07). Furthermore, in All Recipients and Recipients Used Non LD Induction, the risk of rejection was lower with belatacept + tacrolimus treatment compared to belatacept alone, and was suggestively lower in BENEFIT-eligible Recipients and BENEFIT-EXT-eligible

Recipients. Only in the Recipients Used LD Induction Drugs group did there not appear to be a benefit of adding tacrolimus of belatacept. Multivariate analysis could not be performed on the high PRA group due to insufficient patient numbers.

Renal function

Figure 2 shows the comparison of eGFR at 1 year between the three drug regimens for all recipients, BENEFIT-eligible recipients, and BENEFIT-EXT-eligible recipients. The eGFR was significantly higher in the belatacept+tacrolimus and belatacept alone-treated recipients than in the tacrolimus alone-treated recipients in all recipients (64.1 vs 63.5 vs 58.6 mL/min/1.73m^2, respectively, P=.0015) and in the BENEFIT-EXT-eligible group (65.6 vs 60.4 vs 54.3 mL/min/1.73m^2, respectively, P=.0003), although no significant differences were seen in the BENEFIT-eligible recipients (62.6 vs 63 vs 60 mL/min/1.73m^2, respectively, P=.13). There were no significant differences in eGFR between belatacept+tacrolimus and belatacept alone patients in all subgroups.

New onset diabetes and malignancy

Figure 3 compares the incidences of NODAT, *de novo* PTLD, and other new onset malignancy between the three-drug regimens for all recipients based on data at 1 year post-transplant follow up. The incidence of NODAT was significantly lower in the belatacept+tacrolimus and belatacept alone groups than in the tacrolimus alone group (1.7% vs 2.2% vs 3.8%, respectively, P=.01). The incidences of *de novo* PTLD or other new onset malignancy were similar in the three comparison groups. None of the belatacept-treated patients who developed PTLD were EBV seronegative or received LD induction therapy.

Discussion

In the current study, the absolute rates of one-year BPAR in belatacept alone-treated patients were similar to those reported in the two clinical trials (16.7% and 18.6% in BENEFIT-eligible and BENEFIT-EXT-eligible, respectively, compared to 17% and 17.7% for the BENEFIT and BENEFIT-EXT trials, respectively), although the belatacept alone-treated patients had significantly higher BPAR rates compared to the tacrolimus alone-treated recipients in all study groups. Furthermore, in belatacept alone-treated recipients treated with a non-LD induction drug, the absolute one-year BPAR rate was higher at 23.1%. Treatment with a non-LD induction drug but addition of tacrolimus to the belatacept regimen (belatacept+tacrolimus-treated recipients) at discharge reduced the one-year BPAR rejection rate down to 16.5%. The belatacept+tacrolimus-treated patients who received LD induction were at higher risk for rejection than belatacept alone-treated patients, which likely explains this group having the highest absolute rejection rate in all recipients receiving LD induction (20.7%). Indeed, multivariate analysis demonstrated no significant difference in hazard ratios for rejection between belatacept+tacrolimus and tacrolimus alone patients with LD induction and in all groups studied. However, BPAR rates in the belatacept+tacrolimus-treated patients who received LD induction are suggestively higher than in those treated with tacrolimus alone, although the group comprised only 29 patients. Further investigation with larger sample size is clearly needed to be able to draw any further conclusions. In the real clinical setting, there are often high PRA patients, who were excluded from the clinical trials. In fact, the highest absolute rate of rejection was observed in the high PRA patients who did not receive LD induction (43%). Taken in sum, the data regarding rejection in this study would suggest caution with the use of

belatacept alone and strong consideration of LD induction or addition of tacrolimus for the first year post-transplant, especially in recipients with a high baseline risk for rejection.

At 12 months, renal function was superior in patients receiving belatacept versus cyclosporine in both the BENEFIT -and BENEFIT-EXT trials (9, 10). In the current study, renal function was no different between belatacept+tacrolimus, belatacept alone-, and tacrolimus-treated patients at 12 months in the patients meeting BENEFIT criteria. However, in those patients meeting BENEFIT-EXT criteria, renal function was significantly greater in belatacept+tacrolimus- and belatacept alone- versus tacrolimus alone-treated patients. In patients meeting BENEFIT or BENEFIT-EXT criteria, renal function in the tacrolimus alone-treated patients (60 and 54 mL/min/1.73M^2, respectively) was observed to be numerically higher than that reported for the cyclosporine-treated patients in the BENEFIT and BENEFIT-EXT trials (50 and 45 mL/min/1.73M^2, respectively).

In both the BENEFIT and BENEFIT-EXT trials, belatacept was associated with significant improvement in cardiometabolic complications of blood pressure and lipid control compared to cyclosporine, and in the BENEFIT-EXT trial, a significant reduction in incidence of NODAT was also reported. In the current study, only the incidence of NODAT could be assessed, since the SRTR database does not contain measurements for blood pressure or lipid levels. In both belatacept-treated groups, the one-year incidence of NODAT was significantly lower in comparison to tacrolimus alone-treated patients. It therefore does not appear that tacrolimus as used in the belatacept+tacrolimus group incurs the same risk for NODAT as with the standard usage of the drug, which along with the eGFR results, leads one to speculate that the combined regimen involved lower goal tacrolimus levels, especially since steroid use was significantly higher in this group.

In the BENEFIT and BENEFIT-EXT trials, 1.0% of patients receiving the approved dosage developed PTLD during the first year compared to 0.2% of those who received cyclosporine, with most of the cases in EBV seronegative patients. In the current study, only 0.22% of belatacept-

treated (>94% EBV seropositive) versus 0.13% of tacrolimus alone-treated patients developed PTLD in this same time frame, which may reflect greater awareness among clinicians of the role EBV seropositivity plays in the proper selection of belatacept candidates to decrease this risk. A total of 9 other new onset malignancies occurred during one-year follow up in belatacept+tacrolimus (0.5%) and belatacept alone groups (1.5%), which were not statistically different with the tacrolimus alone group (1.2%).

The major strength of this study is the large study population available through use of the nationwide SRTR dataset, which enhances generalizability of the study findings and provides the power for precision of the statistical analyses. The limitations of this study include missing post-transplant follow up data for the primary outcomes and the lack of data on important secondary outcomes, such as blood pressure, lipid panel measurements, and infection diagnoses. The immunosuppressant drug dosage and trough levels are not collected by the SRTR, and similarly, the types of acute rejection cannot be ascertained. Information is also lacking on the presence of donor specific antibodies and whether protocol or for cause biopsies were performed at each individual center.

Conclusion

Despite a higher rate of acute rejection, belatacept alone use was associated with non-inferior effects on composite patient death or one-year graft loss outcome compared with tacrolimus alone use in a real clinical setting. The acute rejection rates were particularly high in those recipients with high PRA who did not receive LD induction. Belatacept use resulted in significantly higher renal function at 1 year compared to tacrolimus in BENEFIT-EXT eligible recipients of kidneys from marginal donors. It is unknown at this time whether the superior graft function at 1 year will translate into better long-term graft survival in this cohort. Finally a significantly lower incidence of NODAT was observed with belatacept use, even when combined with

tacrolimus during parts of the first year. It may be advisable to add short-term tacrolimus to belatacept during the first year post-transplant and consider LD induction in all but the lowest risk patients, as the risk to benefit ratio allows.

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Disclaimer

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Figure Legends

Figure 1. (A) Comparison of unadjusted one-year BPAR rates between three drug regimens in All Recipients, BENEFIT-eligible Recipients, and BENEFIT-EXT-eligible Recipients. The rates of one-year BPAR were numerically similar between belatacept+tacrolimus- and belatacept alone- treated KTR in the overall study population, BENEFIT-eligible patients, and BENEFIT-EXT-eligible patients. However, these rejection rates (in the belatacept+tacrolimus- and belatacept alone-treated KTR) were significantly higher than those in the tacrolimus alone-treated KTR across the three comparison groups. BPAR, biopsy-proven acute rejection; KTR, kidney transplant recipients. (B) Comparison of one-year unadjusted BPAR rates between three drug regimens in patients receiving lymphocyte-depleting and non lymphocyte-depleting induction. The use of lymphocyte depleting induction drugs was associated with lower one-year BPAR rates in the recipients who received belatacept-alone, whereas these rates were higher in belatacept+tacrolimus recipients. The lowest rejection rates were observed in the tacrolimus-alone group with either induction agent. BPAR, biopsy-proven acute rejection; KTR, kidney transplant recipients.

Figure 2. Comparison of eGFR at 1 year between three drug regimens in All Recipients, BENEFIT-eligible Recipients, and BENEFIT-EXT-eligible Recipients. The eGFR was significantly higher in the belatacept+tacrolimus or belatacept alone-treated recipients than in the tacrolimus alone-treated recipients in all recipients and in the BENEFIT-EXT-eligible group, although no significant differences were seen in the BENEFIT-eligible recipients. There were no significant differences in eGFR between belatacept+tacrolimus and belatacept alone in either subgroup. KTR, kidney transplant recipients; eGFR, estimated glomerular filtration rate.

Figure 3. Comparison of metabolic and malignancy outcomes at 1 year between three drug regimens. The incidence of NODAT was significantly lower in the two belatacept groups than in the tacrolimus-alone group. The incidences of *de novo* PTLD or other new onset malignancy were similar in the three comparison groups. KTR, kidney transplant recipients; NODAT, new onset diabetes after transplantation; PTLD, post-transplant lymphoproliferative disease; KTR, kidney transplant recipients.

References

1. Bodell M, Womer K, Rabb H. Immunosuppressive Medications in Kidney Transplantation. In: Richard J. Johnson M, John Feehally, DM, FRCP, and Jurgen Floege, MD, FERA, editor. Comprehensive Clinical Nephrology. 5th ed. St. Louis, Missouri: Saunders; 2015.

2. Matas AJ, Smith JM, Skeans MA, Thompson B, Gustafson SK, Schnitzler MA, et al. OPTN/SRTR 2012 Annual Data Report: kidney. Am J Transplant. 2014;14 Suppl 1:11-44.

3. Tantravahi J, Womer KL, Kaplan B. Why hasn't eliminating acute rejection improved graft survival? Annu Rev Med. 2007;58:369-85.

4. Gaston RS, Cecka JM, Kasiske BL, Fieberg AM, Leduc R, Cosio FC, et al. Evidence for antibody-mediated injury as a major determinant of late kidney allograft failure. Transplantation. 2010;90(1):68-74.

5. Sellares J, de Freitas DG, Mengel M, Reeve J, Einecke G, Sis B, et al. Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. Am J Transplant. 2012;12(2):388-99.

6. Stegall MD, Gaston RS, Cosio FG, Matas A. Through a glass darkly: seeking clarity in preventing late kidney transplant failure. J Am Soc Nephrol. 2015;26(1):20-9.

7. Guerra G, Srinivas TR, Meier-Kriesche HU. Calcineurin inhibitor-free immunosuppression in kidney transplantation. Transpl Int. 2007;20(10):813-27.

8. Gupta G, Womer KL. Profile of belatacept and its potential role in prevention of graft rejection following renal transplantation. Drug Des Devel Ther. 2010;4:375-82.

9. 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.

10. 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.

11. 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.

Table 1. Demographic and clinical characteristics of study populations

Characteristics	Belatacept- and Tacrolimus-Treated KTR N=417	Belatacept Alone-Treated KTR N=458	Tacrolimus Alone-Treated KTR N=49 369	P Value
Recipient Age, Years, Mean ± SD	51.5 ± 13.1	53.7 ± 13.9	51.9 ± 13.6	.017
Recipient African American Race, N (%)	204 (49)	105 (23)	12 283 (25)	<.0001
Recipient Female Gender, N (%)	174 (42)	155 (34)	19 091 (39)	.05
Dialysis Length Pre-transplant, N (%)				<.0001
Preemptive	55 (13)	90 (20)	9185 (19)	
0-2 Years	90 (22)	138 (30)	14 334 (29)	
> 2 Years	272 (65)	230 (50)	25 850 (52)	
Recipient BMI>30, N (%)	128 (31)	163 (36)	16906 (34)	.0017
Cause of ESRD, N (%)				.04
Hypertension	99 (24)	107 (23)	10 987 (22)	
Diabetes	112 (27)	124 (27)	12 980 (26)	

Glomerulonephritis Polycystic Kidney Disease Other	110 (26) 35 (8) 61 (15)	95 (21) 54 (12) 78 (17)	10 661 (22) 4792 (10) 9949 (20)	
Donor Age, Years, Mean ± SD	39.0 ± 15.6	43.6 ± 14.6	39.5 ± 14.9	<.0001
Donor Female Gender, N (%)	227 (54)	236 (52)	23 192 (47)	.0016
Donor African American Race, N (%)	118 (28)	67 (15)	6605 (13)	<.0001
Donor Type by OPTN, N (%) Living Donor Standard Criteria Donor OPTN Extended Criteria Donor*	 143 (34) 238 (57) 36 (9)	 186 (41) 208 (45) 64 (14)	 16 408 (33) 28 096 (57) 4865 (10)	<.0001
Donor Type by BENEFIT Trials Criteria**, N (%) BENEFIT-eligible Donors BENEFIT-EXT-eligible Donors High PRA Recipients	 236 (57) 105 (25) 76 (18)	 299 (65) 126 (28) 33 (7.2)	 29 253 (59) 13 310 (27) 6806 (14)	<.0001
Donor Death Due to Cerebrovascular Accident, N (%)	49 (18)	43 (16)	4709 (14)	.19
Donor Hypertension, N (%)	91 (22)	107 (23)	10 031 (20)	.21
Donor Diabetes, N (%)	154 (37)	205 (45)	19 003 (38)	.02
Recipient PRA, N (%) 0~20 20~50 50~80 ≥80	 247 (62) 60 (15) 37 (9) 56 (14)	 319 (78) 49 (12) 15 (4) 25 (6)	 30 827 (68) 5 402 (12) 3 861 (9) 5 030 (11)	<.0001
Recipient Epstein-Barr Virus Seropositivity, N (%)	410 (98)	431 (94)	38 011 (77)	<.0001
HLA Mismatch >3, N (%)	286 (69)	293 (64)	32 008 (65)	<.0001
Cold Ischemia Time, Hours, Mean ± SD	11.4 ± 8.8	12.1 ± 10.0	12.4 ± 10.3	.09
Delayed Graft Function, N (%)	82 (20)	91 (20)	8554 (17)	.17
Induction with LD Agents, N (%)	29 (7)	233 (51)	33 228 (67)	<.0001
Steroid Use at Discharge, N (%)	384 (92)	354 (77)	34 633 (70)	<.0001
Mycophenolate Mofetil Use at Discharge, N (%)	411 (99)	423 (92)	47 963 (97)	<.001
Sirolimus Use at Discharge, N (%)	0 (0)	22 (4.8)	470 (1)	<.0001
Recipient with Cardiovascular Disease, N (%)	44 (11)	56 (12)	4578 (9)	.02
Recipient Previous Malignancy, N (%)	35 (8)	50 (11)	3452 (7)	.003
Recipient Primary Insurance, Private, N (%)	110 (26)	170 (37)	17 476 (35)	<.0001
Recipients with Previous Kidney Transplant, N (%)	42 (10)	23 (5)	5931 (12)	<.0001

Recipient Physical Capacity with Limitation, N (%)	385 (92)	402 (88)	39 969 (81)	<.0001
Recipient Serum Creatinine at Discharge, Mean ± SD	3.1 ± 2.6	3.2 ± 3.0	2.9 ± 2.6	.01
Kidney Transplant Center, N (%) Major Belatacept Center	377 (90)	126 (28)	214 (43)	<.0001
Mean Follow Up (Months), Mean ± SD	8.7 ± 7.0	10 ± 9	12.9 ± 10.2	<.0001
Year of Transplant, N (%)***				<.0001
2011	2 (0.5)	62 (13.5)	8716 (17.7)	
2012	126 (30.2)	109 (23.8)	14 234 (28.8)	
2013	159 (38.1)	132 (28.8)	14 744 (29.9)	
2014	130 (31.2)	155 (33.8)	11 675 (23.7)	

*: OPTN Extended Criteria Donor, defined as donors ≥60 years old; or donors ≥50 years old and who had at least two other risk factors (hypertension, death from cerebrovascular accident, or serum creatinine >1.5mg/dL).

**: (i) BENEFIT-eligible Donor, defined as living donors and non extended criteria deceased donors with cold ischemia time of <24 hours. Excluded were donation after cardiac death deceased donors, first-time transplants with a PRA ≥50%, and re-transplants with a PRA ≥30%.
(ii) BENEFIT-EXT-eligible Donor, defined as donors ≥60 years old; or donors ≥50 years old and who had at least two other risk factors (hypertension, death from cerebrovascular accident, or serum creatinine >1.5mg/dL); or cold ischemia time of ≥24 hours; or donation after cardiovascular death.
(iii) High PRA Recipients are first-time patients with a panel reactive antibody ≥50% or re-transplants with a panel reactive antibody ≥30%.

***: Column percent adds to 100%.

KTR, kidney transplant recipients; SD, standard deviation; BMI, body mass index; ESRD, end stage renal disease; PRA, panel reactive antibody; HLA, human leukocyte antigen; LD, lymphocyte-depleting; OPTN, Organ Procurement and Transplantation Network.

Table 2: Patient/Graft Survival in All Recipients, BENEFIT-eligible Recipients, BENEFIT-EXT-eligible Recipients, and High PRA Recipients.

Patient Groups	Month 12 Endpoints	Belatacept+ Tacrolimus N (%)	Belatacept Alone N (%)	Tacrolimus Alone N (%)
All Recipients	Number of Patients	N=417	N=458	N=49 369
	Graft Loss or Death, N (%)	13 (3.1)	17 (3.7)	2002 (4.1)
	Death Censored Graft Loss	6 (1.4)	7 (1.5)	1067 (2.2)
	Death	9 (2.2)	12 (2.6)	1154 (2.3)
	Death with Functioning Graft	7 (1.7)	10 (2.2)	982 (2.0)

BENEFIT-eligible Recipients*	Number of Patients	N=236	N=299	N=29 253
	Graft Loss or Death, N (%)	7 (3)	10 (3.3)	894 (3.1)
	Death Censored Graft Loss	3 (1.3)	4 (1.3)	453 (1.6)
	Death	4 (1.7)	7 (2.3)	530 (1.8)
	Death with Functioning Graft	4 (1.7)	6 (2.0)	466 (1.6)
BENEFIT-EXT- eligible Recipients**	Number of Patients	N=105	N=126	N=13 310
	Graft Loss or Death, N (%)	4 (3.8)	6 (4.8)	842 (6.3)
	Death Censored Graft loss	2 (1.9)	2 (1.6)	463 (3.5)
	Death	3 (2.9)	5 (4.0)	486 (3.7)
	Death with Functioning graft	2 (1.9)	4 (3.2)	396 (3.0)
High PRA Recipients***	Number of Patients	N=76	N=33	N=6806
	Graft Loss or Death, N (%)	2 (2.6)	1 (3.0)	266 (3.9)
	Death Censored Graft Loss	1 (1.3)	1 (3.0)	151 (2.2)
	Death	2 (2.6)	0 (0.0)	138 (2.0)
	Death with Functioning Graft	1 (1.3)	0 (0)	120 (1.8)

* BENEFIT-eligible Donor, defined as living donors and non extended criteria deceased donors with cold ischemia time of <24 hours. Excluded were donation after cardiac death deceased donors, first-time transplants with a PRA ≥50%, and re-transplants with a PRA ≥30%.

**BENEFIT-EXT-eligible Donor, defined as donors ≥60 years old; or donors ≥50 years old and who had at least two other risk factors (hypertension, death from cerebrovascular accident, or serum creatinine >1.5mg/dL); or cold ischemia time of ≥24 hours; or donation after cardiovascular death

***High PRA Recipients are first-time patients with a panel reactive antibody ≥50% or re-transplants with a panel reactive antibody ≥30%

PRA, panel reactive antibody.

Table 3. Adjusted hazard ratios for one-year BPAR

Outcomes	Groups	Adjusted Hazard Ratio (95% CI, P value)		
		Belatacept+Tacrolimus vs Tacrolimus Alone	Belatacept Alone vs Tacrolimus Alone	Belatacept+Tacrolimus vs Belatacept Alone
One-Year Biopsy Proven Acute Rejection	All Recipients	1.33 (0.93 – 1.90, P=.12)	2.36 (1.82 – 3.05, P<.0001)	0.54 (0.36 – 0.81, P=0.003)
	Recipients Used Lymphocyte- Depleting Induction Drugs	2.35 (0.94 – 5.90, P=.07)	1.86 (1.20 – 2.90, P=.006)	1.50 (0.51 – 4.41, P=0.47)
	Recipients Used Non Lymphocyte- Depleting Induction Drugs	1.39 (0.93 – 2.08, P=.11)	2.65 (1.90 – 3.70, P<.0001)	0.50 (0.32 – 0.76, P=0.001)
	BENEFIT-eligible Recipients	1.65 (0.98 – 2.78, P=.06)	2.51 (1.79 – 3.52, P<.0001)	0.64 (0.35 – 1.15, P=0.13)
	BENEFIT-EXT-eligible Recipients	0.73 (0.38 – 1.40, P=.35)	1.74 (1.06 – 2.85, P=.027)	0.41 (0.18 – 0.96, P=0.04)

Critical P value is .017 due to Bonferroni adjustment for multiple comparisons.

Other covariates adjusted in the model include: recipient age, race, gender, steroid use at hospital discharge, mycophenolate mofetil use at hospital discharge, panel reactive antibody, pre-transplant dialysis duration, HLA mismatch, recipient insurance, and recipient Epstein-Barr virus infection. Donor characteristics were: donor age, and donor types.

Induction with lymphocyte-depleting agents was only adjusted in the multivariate model for All Recipients, BENEFIT-eligible Recipients, and BENEFIT-EXT-eligible recipients. For the subgroup analyses in Patients used Lymphocyte-Depleting Induction Drugs or Recipients Used Non Lymphocyte-Depleting Induction Drugs, choice of induction agent was not adjusted in the multivariate model.

BPAR, biopsy proven acute rejection; CI, confidence interval.

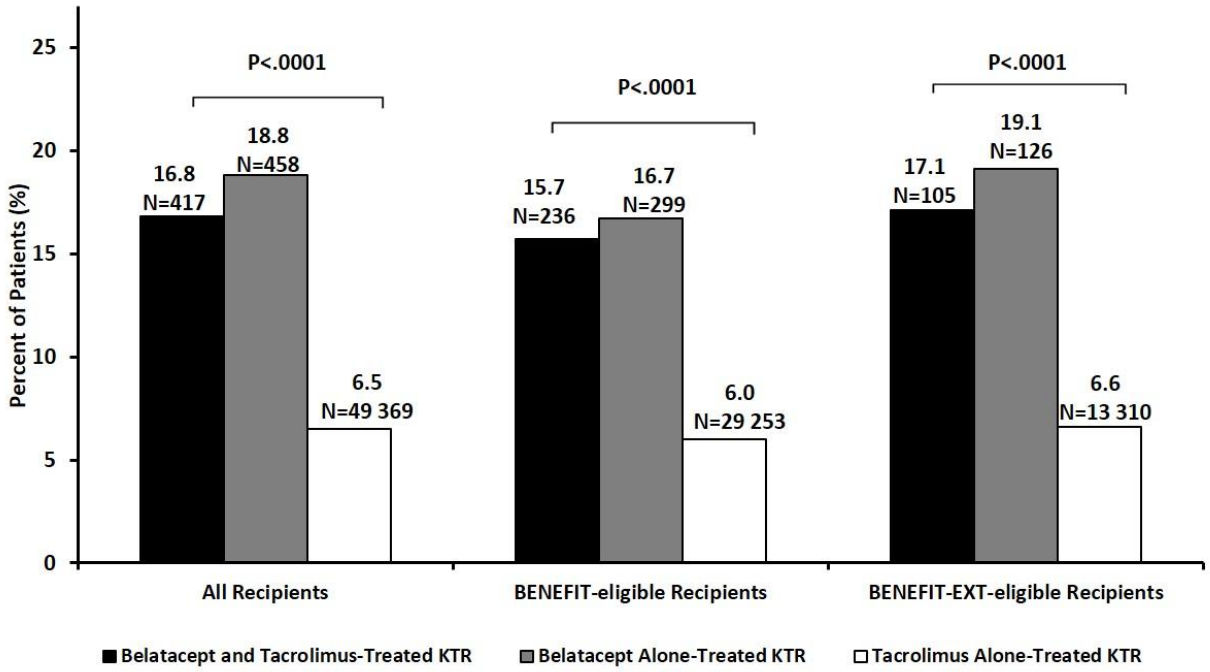


Figure 1. a) Comparison of unadjusted one-year BPAR rates between three drug regimens in All Recipients, BENEFIT-eligible Recipients, and BENEFIT-EXT-eligible Recipients. The rates of one-year BPAR were numerically similar between belatacept+tacrolimus- and belatacept alone- treated KTR in the overall study population, BENEFIT-eligible patients, and BENEFIT-EXT-eligible patients. However, these rejection rates (in the belatacept+tacrolimus- and belatacept alone-treated KTR) were significantly higher than those in the tacrolimus alone-treated KTR across the three comparison groups. BPAR, biopsy-proven acute rejection; KTR, kidney transplant recipients.

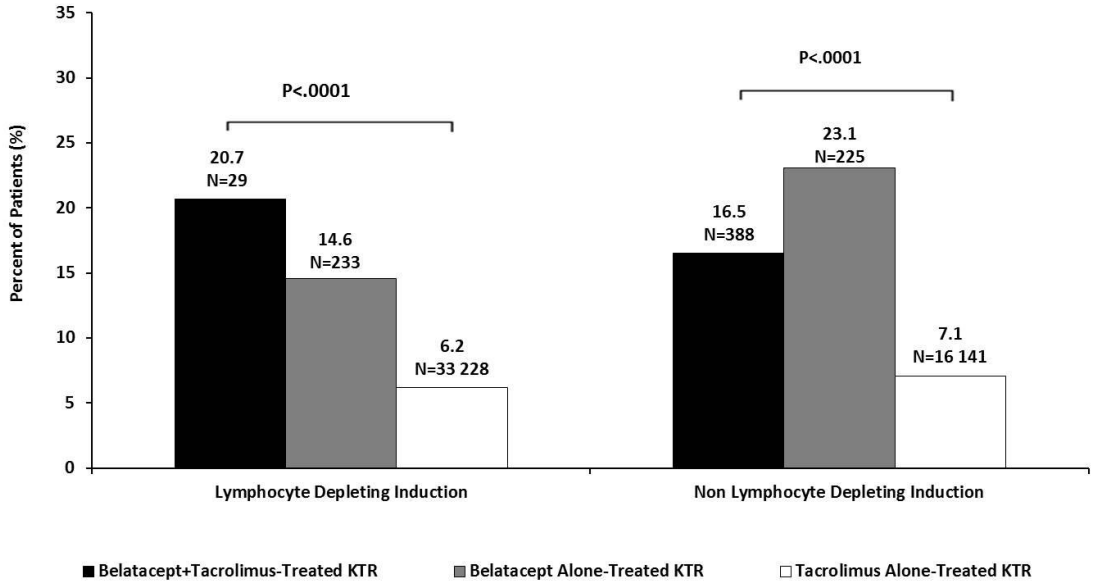
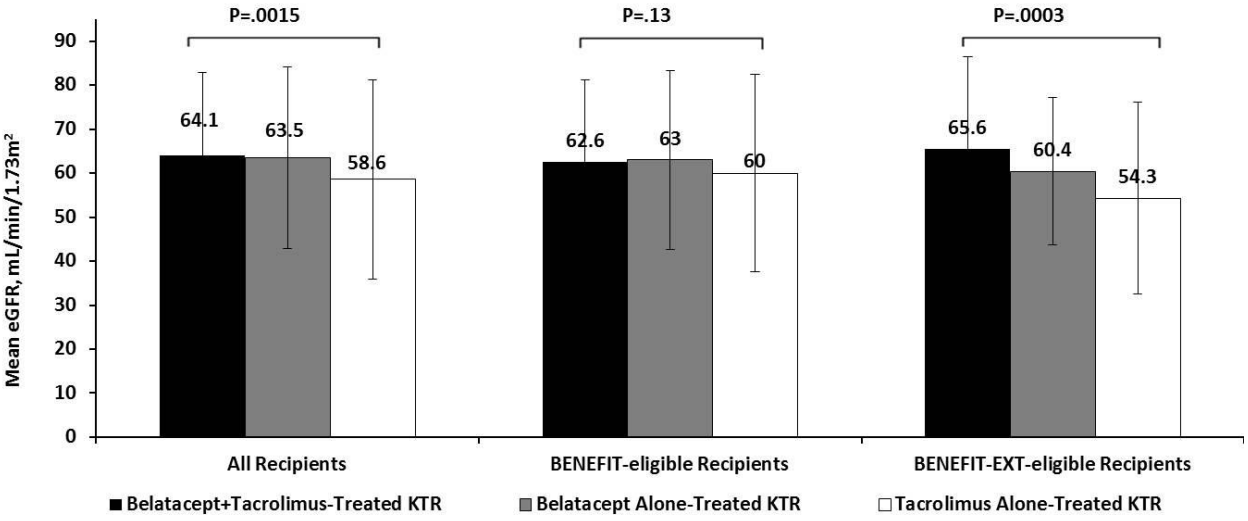


Figure 1. b) Comparison of one-year unadjusted BPAR rates between three drug regimens in patients receiving lymphocyte-depleting and non lymphocyte-depleting induction. The use of lymphocyte depleting induction drugs was associated with lower one-year BPAR rates in the recipients who received belatacept-alone, whereas these rates were higher in belatacept+tacrolimus recipients. The lowest rejection rates were observed in the tacrolimus-alone group with either induction agent. BPAR, biopsy-proven acute rejection; KTR, kidney transplant recipients.



Recipients at 1 Year

Groups	All Recipients	BENEFIT-eligible Recipients	BENEFIT-EXT-eligible Recipients
Belatacept+Tacrolimus-Treated KTR	195	115	46
Belatacept Alone-Treated KTR	218	143	58
Tacrolimus Alone-Treated KTR	32 480	19 339	8530

Figure 2. Comparison of eGFR at 1 year between three drug regimens in All Recipients, BENEFIT-eligible Recipients, and BENEFIT-EXT-eligible Recipients. The eGFR was significantly higher in the belatacept+tacrolimus or belatacept alone-treated recipients than in the tacrolimus alone-treated recipients in all recipients and in the BENEFIT-EXT-eligible group, although no significant differences

were seen in the BENEFIT-eligible recipients. There were no significant differences in eGFR between belatacept+tacrolimus and belatacept alone in either subgroup. KTR, kidney transplant recipients; eGFR, estimated glomerular filtration rate.

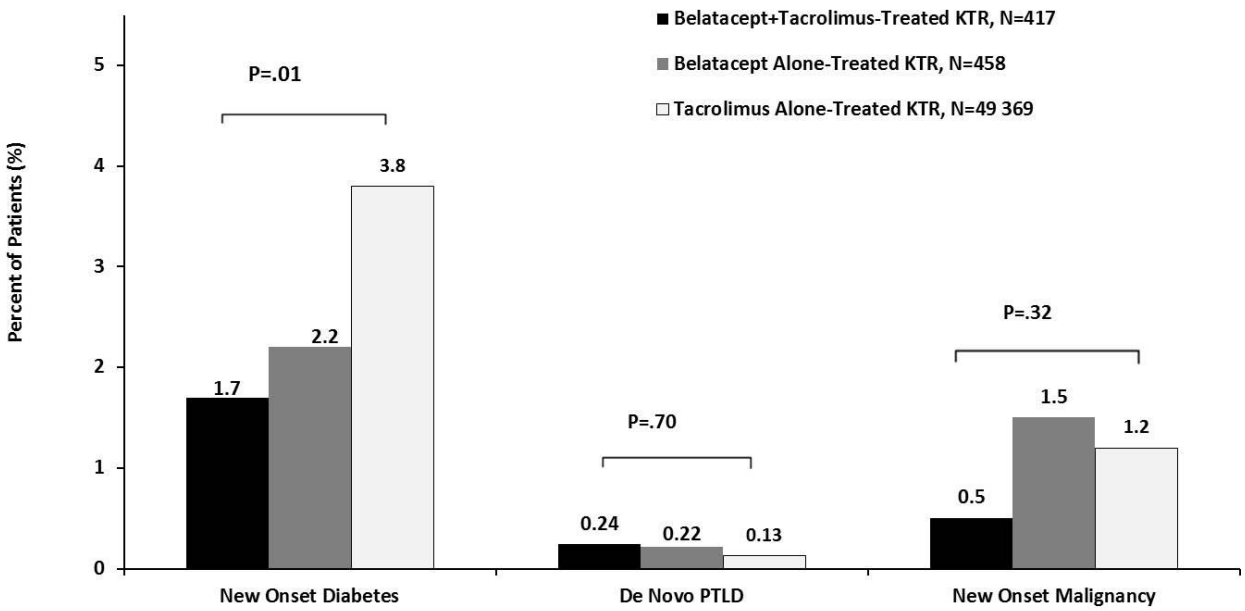


Figure 3. Comparison of metabolic and malignancy outcomes at 1 year between three drug regimens. The incidence of NODAT was significantly lower in the two belatacept groups than in the tacrolimus-alone group. The incidences of *de novo* PTLD or other new onset malignancy were similar in the three comparison groups. KTR, kidney transplant recipients; NODAT, new onset diabetes after transplantation; PTLD, post-transplant lymphoproliferative disease; KTR, kidney transplant recipients.