HHS Public Access

Author manuscript

Transplantation. Author manuscript; available in PMC 2022 September 01.

Published in final edited form as:

Transplantation. 2021 September 01; 105(9): 2119–2123. doi:10.1097/TP.0000000000003824.

Immunogenicity and Reactogenicity after SARS-CoV-2 mRNA Vaccination in Kidney Transplant Recipients Taking Belatacept

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Abstract

Background.—Belatacept may impair humoral immunity, impacting the effectiveness of SARS-CoV-2 mRNA vaccines in transplant recipients. We investigated immunogenicity after SARS-CoV-2 mRNA vaccines in kidney transplant recipients who are and are not taking belatacept.

Methods.—Participants were recruited between 12/9/2020 – 4/1/2021. Blood samples were collected after dose 1 and dose 2 (D1, D2), and analyzed using either an anti-SARS-CoV-2 enzyme immunoassay against the S1 domain of the SARS-CoV-2 spike protein or immunoassay

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Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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DISCLOSURES

The authors of this manuscript have the following conflicts of interest to disclose as described by *Transplantation*: Dorry L. Segev, MD PhD has the following financial disclosures: consulting and speaking honoraria from Sanofi, Novartis, CSL Behring, Jazz Pharmaceuticals, Veloxis, Mallincrodt, Thermo Fisher Scientific. Robin Avery, MD has the following financial disclosures: study/grant support from Aicuris, Astellas, Chimerix, Merck, Oxford Immunotec, Qiagen, and Takeda/Shire.

against the receptor-binding domain of the SARS-CoV-2 spike protein. Stabilized inverse probability of treatment weights (IPTW) was used to compare immunogenicity and a weighted logistics regression was used to calculate fold change of positive response.

Results.—Among the 609 participants studied, 24 (4%) were taking belatacept. After dose 1, 0/24 (0%) belatacept patients had detectable antibodies, compared to 77/568 (14%) among the equivalent non-belatacept population (p=0.06). After dose 2, 1/19 (5%) belatacept patients had detectable antibodies, compared to 190/381 (50%) among the equivalent non-belatacept population (p<0.001). Belatacept use was associated with 16.7-fold lower odds of having a positive post-D2 titer result (p <0.01).

Conclusions.—Additional measures need to be explored in order to protect kidney transplant recipients taking belatacept. Best safety practices should be continued despite vaccination among this population.

Keywords

COVID-19; SARS-CoV-2; mRNA vaccination; belatacept

1. INTRODUCTION

Impaired humoral immunity may impact the effectiveness of SARS-CoV-2 mRNA vaccines in transplant recipients. In fact, poor anti-spike antibody response after the first dose of a mRNA SARS-CoV-2 vaccine among solid organ transplant recipients has been demonstrated and was associated with immunosuppression regimens containing anti-metabolites.[1] However, understanding of antibody response after vaccination in recipients taking selective costimulation blockers such as belatacept remains limited.[2]

Belatacept, which is a selective inhibitor of T-cell costimulation through interference with the CD28-CD80/86 pathway and is often used as a “renal-sparing” immunosuppressive drug, causes impairment of T follicular helper cell/B cell crosstalk and regulates B cell pathways.[3] It has been shown to directly decrease plasmablast differentiation and IgG secretion in both *in vitro* models and *in vivo* data.[4] We hypothesized that belatacept, due to its unique mechanism of action, may result in a poor antibody response after SARS-CoV-2 mRNA vaccination.

To investigate this, we studied kidney transplant recipients who received a SARS-CoV-2 mRNA vaccine and sought to compare the post-vaccine immunogenicity of recipients who take belatacept as part of their immunosuppression regimen to those who do not. We also investigated the reactogenicity and safety of kidney recipients after vaccination.

2. METHODS

2.1 Study population and data source

Kidney transplant recipients were recruited through social media or their transplant team between December 9, 2020 – April 1, 2021. All English-speaking participants ≥18 years old who received a mRNA SARS-CoV-2 vaccine were eligible to be enrolled in the study. Those were who were previously diagnosed with COVID-19 or tested positive for SARS-CoV-2

anti-spike antibodies prior to vaccination were excluded. Participant characteristics such age, sex, immunosuppression regimen, other transplant types, years since transplant, and body mass index were captured using Research Electronic Data Capture (REDCap) hosted by Johns Hopkins.[5,6] This study was approved by the institutional review board at the Johns Hopkins School of Medicine (IRB00248540) and adheres to principles of Declaration of Helsinki; participants were consented electronically.

2.2 SARS-CoV-2 vaccine immunogenicity

Blood samples were collected after dose 1 and dose 2 (D1, D2) using either the TAP II Seventh Sense Biosystems blood collection device (Medford, MA) or standard venipuncture.[7] Samples collected using the TAP II device were analyzed using an enzyme immunoassay that tests for antibodies to the S1 domain of the SARS-CoV-2 spike protein (EUROIMMUN, Lübeck, Germany), with a positive cutoff of ≥1.1 arbitrary units (AU) (sensitivity of 87.0%, specificity of 97.5%).[8] Samples collected via standard venipuncture were analyzed using an anti-SARS-CoV-2 S enzyme immunoassay that tests for antibodies against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein (Roche Elecsys, Rotkreuz, Switzerland), with a positive cutoff of ≥0.8 U/mL (sensitivity of 84.0%, specificity of 100%).[9] There were 17 individuals with a missing sample for D1 and a negative result for D2; for these individuals, the result for D1 was imputed to be negative.

2.3 SARS-CoV-2 vaccine reactogenicity

Questionnaires were distributed 7 days after D1 and D2.[10] After each dose, participants were asked if they experienced any local symptoms such as pain, swelling, or erythema, or any systemic symptoms such as fever, fatigue, headaches, chills, vomiting, diarrhea, or myalgias. Participants were asked to rate their symptoms on an ordinal scale of none, mild, moderate, or severe. Mild symptoms were defined as symptoms that did not interfere with daily activities, whereas moderate symptoms were defined as those that caused some interference with daily activity, and severe symptoms were defined as those that prevented daily activity.

2.4 Safety of SARS-CoV-2 vaccines

After D1 and D2, participants were asked to report any development of anaphylaxis requiring epinephrine, new diagnoses of COVID-19 infection, incident neurological conditions such as Guillain-Barré syndrome or Bell's palsy, other infections requiring treatment, or new onset of acute rejection. Participants were also invited to report any other medical illnesses in addition to those specifically asked.

2.5 Statistical analysis

Participant demographic and clinical characteristics were compared between kidney transplant recipients with an immunosuppression regimen that contains belatacept vs. a regimen that does not contain belatacept using a Wilcoxon rank-sum test for continuous variables and Fisher’s exact test for binary or categorical variables.

We could not compare immunogenicity of belatacept vs. non-belatacept patients after the first vaccine dose using standard regression techniques, because zero belatacept

patients had a positive result. Therefore, to compare immunogenicity between the two groups accounting for potential confounding, we modeled chance of having a positive result among the non-belatacept patients using logistic regression and adjusting for age, years since transplant, immunosuppression contain anti-metabolites, sex, race, vaccine type, and type of immunoassay performed. We then used this model to calculate an expected number of positive responses among the belatacept patients and compared the observed to expected value, assuming a Poisson distribution to test for statistical significance. Additionally, to compare immunogenicity after the second dose, we calculated stabilized inverse probability of treatment weights (IPTW) weighting on 3 prespecified factors: immunosuppression regimen containing anti-metabolites (mycophenolate mofetil, mycophenolic acid, azathioprine), years since transplant, and participant age; we then performed weighted logistic regression to obtain a fold change of positive response. All analyses were performed using Stata 15.1/SE (College Station, Texas) and we reported p-values with an α of 0.05 for statistical significance.

3. RESULTS

3.1 Population characteristics

We studied 609 kidney transplant recipients, of which 24 (4%) recipients were on immunosuppression regimens containing belatacept and 585 were not taking belatacept (96%) (Table 1). Median (interquartile range [IQR]) age was 58 (45 – 68) years, 60% were women, and 13% were non-white. Besides a kidney transplant, other organs transplanted included pancreas (6%), liver (4%), heart (2%), and lung (1%), at a median (IQR) of 7 (3 - 15) years since transplant. Maintenance immunosuppression regimens also included prednisone (68%), mycophenolate (72%), tacrolimus (77%), azathioprine (10%), and sirolimus (8%).

3.2 Immunogenicity after SARS-CoV-2 vaccination

After D1, 0/24 (0%) belatacept patients had detectable antibodies, compared to 77/568 (14%) among the equivalent non-belatacept population (p=0.06). After dose 2, 1/19 (5%) belatacept patients had detectable antibodies, compared to 190/381 (50%) among the equivalent non-belatacept population (p<0.001) (Table 1). Among those who tested positive in the non-belatacept population after D1, the median (IQR) IgG titer level was 2.33 (1.68 – 4.77) AU using the anti-S1 spike assay, and 4.24 (1.81 – 15.05) U/mL using the anti-RBD assay. Among those who tested positive in the non-belatacept population after D2, the median (IQR) IgG titer level was 6.23 (3.12 – 8.74) AU using the anti-S1 assay, and 78.10 (7.42 – 250) U/mL using the anti-RBD assay. The single participant taking belatacept with a detectable antibody level of 48.07 U/ml was a female kidney transplant recipient 5 years out from transplant.

In adjusted analysis, the observed number of positive responses in the belatacept cohort after D1 (0) was statistically significantly less than expected (3.14 positives expected, p=0.04). Similarly, after D2 the observed number of responses (1) was statistically significantly less than expected (8.72 positives expected, p<0.01). In weighted logistic regression, belatacept

use was associated with 16.7-fold lower odds of having a positive post-D2 titer result ($p < 0.01$).

3.3 Reactogenicity after SARS-CoV-2 vaccination

Mild-to-moderate pain was the most commonly reported local site reaction for participants taking belatacept, while mild-to-moderate fatigue and headache were the most common systemic reactions (Figure 1). Severe symptoms were rare. There were no statistically significant differences in reactogenicity in patients taking and not taking belatacept (Table 2).

3.4 Safety of SARS-CoV-2 vaccines

There were no reported cases of anaphylaxis, SARS-CoV-2 infection, or episodes of acute rejection. In the non-belatacept cohort after D1, 7 (1%) non-SARS-CoV-2 infections were reported including cytomegalovirus, ear infection, influenza, abscess, and urinary tract infection. The same cohort also reported 10 (2%) infections after D2, including herpes simplex virus, ear infection, pneumonia, abscess, thrush, urinary tract infection, and upper respiratory infection. After D2, there was one report of hearing loss and one report of transverse myelitis, both in the non-belatacept cohort.

4. DISCUSSION

This is first study to compare antibody response after SAR-CoV-2 mRNA vaccination among kidney transplant recipients who do and do not take belatacept as part of their immunosuppression regimen. In this prospective cohort study of 609 kidney transplant recipients, of which 24 (4%) were on immunosuppression regimens containing belatacept, we found that belatacept use was associated with 16.7-fold lower odds of having a positive post-D2 titer result ($p < 0.01$).

Our previous report of 436 transplant recipients demonstrated that anti-metabolite maintenance immunosuppression therapy was associated with a lower likelihood of developing an antibody response (adjusted incidence rate ratio [aIRR] = $_{0.15}0.22_{0.34}$, $p<0.001$).[1] This study controlled for the effects of anti-metabolite therapy via weighted matching and found that belatacept had significant associations with poor antibody responses, unexplained by anti-metabolites. Thus, we hypothesize that the findings observed in this series may be related to the added impairment of the lymphocyte compartment under belatacept therapy affecting direct and T cell dependent mechanisms of antibody production versus *de novo* vaccine antigens. Our findings are similar to a recently published report of 101 patients taking belatacept.[2]

Reactogenicity after the first and second dose were similar to original clinical trials,[11,12] as well as our previous reports not limited to kidney transplant recipients.[10,13] We previously found that transplant recipients who experienced moderate to severe pain and redness were 1.66-fold and 3.92-fold more likely to develop an antibody response.[12] These findings are not surprising as the onset of symptoms represents the physical manifestation of an inflammatory response. The cohort of participants taking belatacept in this study experienced lower levels of moderate-to-severe symptoms, although these findings were

not statistically significant. Additional studies with a larger sample would be interesting to further characterize the correlation between reactogenicity and immunogenicity in participants taking belatacept.

This study includes a national sample of kidney transplant recipients with early and novel information about the immunogenicity and reactogenicity after SARS-CoV-2 vaccination in kidney transplant recipients taking belatacept. Our results are further strengthened through direct comparisons with matched controls not taking belatacept. However, this study is limited by a smaller sample size and is subject to response bias since various information were self-reported. Further investigation with a larger population is needed to further elucidate the impact of belatacept on vaccine response.

In this prospective cohort study, we found that kidney transplant recipients taking belatacept were associated with 16.7-fold lower odds of having a positive post-D2 titer result ($p < 0.01$). Additional measures need to be explored in order to protect this population and best safety practices should be continued despite vaccination.

FUNDING

This research was made possible with generous support of the Ben-Dov family. This work was supported by grant number F32DK124941 (Boyarsky), K01DK101677 (Massie), and K23DK115908 (Garonzik-Wang) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), K24AI144954 (Segev) from National Institute of Allergy and Infectious Diseases (NIAID), and by a grant from the Transplantation and Immunology Research Network of the American Society of Transplantation (Werbel). The analyses described here are the responsibility of the authors alone and do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizations imply endorsement by the US Government.

ABBREVIATIONS

aIRR	adjusted incidence rate ratio
AU	arbitrary units
COVID-19	Coronavirus disease 2019
D1	dose 1
D2	dose 2
IPTW	inverse probability of treatment weights
IQR	interquartile range
mRNA	messenger ribonucleic acid
REDCap	Research Electronic Data Capture
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
U/ml	units per milliliter

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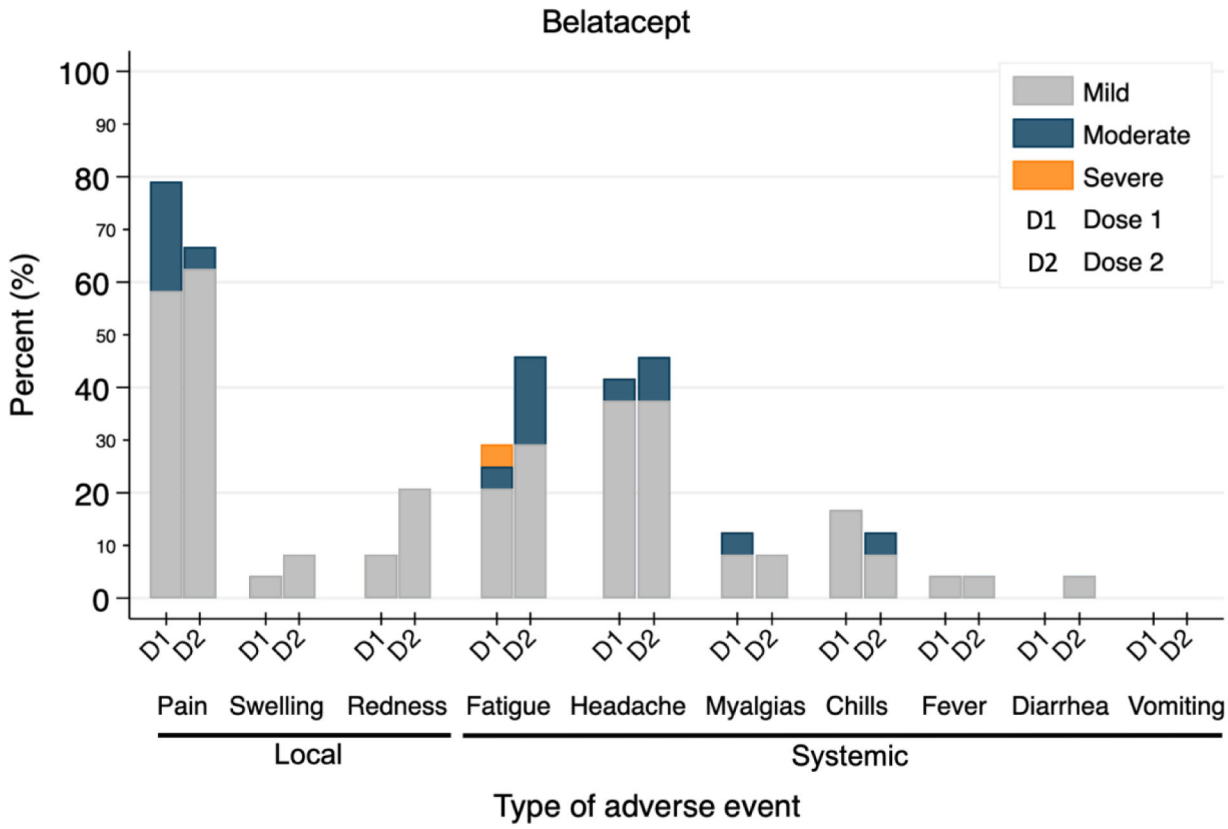

Figure 1.

The development of adverse systems after each SARS-CoV-2 mRNA vaccine dose in kidney transplant recipients taking belatacept.

N= 24, dose 1; 19 dose 2

Table 1:

Baseline characteristics and immunogenicity after SARS-CoV-2 mRNA vaccination in kidney transplant recipients

Participant characteristics	Non-belatacept	Belatacept	P value
	N= 585	N = 24	
Age, median (IQR)	58 (45 - 67)	56 (51 - 66)	0.8
Sex, N (%) female	346 (60)	15 (63)	>0.9
Non-white, N (%)	69 (12)	3 (13)	0.7
BMI, median kg/m^2 (IQR)	26 (23 - 29)	26 (24-29)	0.6
Years since transplant, median (IQR)	8 (3 - 15)	5 (3 -8)	0.02
Other organs transplanted, N (%)			
Pancreas	32 (6)	0 (0)	0.6
Liver	22 (4)	0 (0)	>0.9
Heart	13 (2)	1 (4)	0.4
Lung	6 (1)	0 (0)	>0.9
Other immunosuppression, N (%)			
Prednisone	397 (68)	20 (83)	0.11
Mycophenolate	422 (72)	16 (67)	0.6
Tacrolimus	465 (79)	5 (21)	<0.001
Azathioprine	56 (10)	3 (13)	0.6
Sirolimus	49 (8)	2 (8)	>0.9
Vaccine manufacturer, N (%)			
BNT162b2 (Pfizer/BioNTech)	305 (54)	11 (46)	0.5
mRNA-1273 (Moderna)	260 (46)	13 (54)	
Antibody response after D1, N (%) *			
Positive	77 (14)	0 (0)	0.06
Negative	491 (86)	24 (100)	
IgG level among positives, median (IQR)			
Anti-S1 immunoassay, AU	2.33 (1.68 – 4.77)	N/A	
Anti-RBD immunoassay, U/mL	4.24 (1.81 – 15.05)	N/A	
Days from D1 to blood sample, median (IQR)	21 (19 -26)	22 (19 - 26)	0.8
Antibody response after D2, N (%) **			
Positive	190 (50)	1 (5)	<0.001
Negative	191 (50)	18 (95)	
IgG level among positives, median (IQR)			
Anti-S1 immunoassay, AU	6.23 (3.12 – 8.74)	N/A	
Anti-RBD immunoassay, U/mL	78.10 (7.42 – 250)	48.07 $^{\pm}$	
Days from D2 to blood sample, median (IQR)	29 (28 - 32)	29 (28 - 31)	0.7

* N = 568, non-belatacept; N = 24, belatacept

** N = 381, non-belatacept; N = 19, belatacept

[+] N = 1

Abbreviations: IQR, interquartile range; D1, dose 1; D2, dose 2; AU, arbitrary units; RBD, receptor binding domain; U/mL, units per milliliter

Table 2.

Comparison of reactogenicity after SARS-CoV-2 mRNA vaccination in kidney transplant recipients

Reactogenicity	Non-belatacept	Belatacept	P value
After Dose 1 *			
Moderate/severe local symptoms, %			
Pain	24	22	>0.9
Swelling	2	0	>0.9
Erythema	1	0	>0.9
Moderate/severe systemic symptoms, %			
Fatigue	13	9	0.8
Headache	7	4	>0.9
Myalgias	6	4	>0.9
Chills	3	0	>0.9
Fever	2	0	>0.9
Diarrhea	2	0	>0.9
Vomiting	1	0	>0.9
After Dose 2 **			
Moderate/severe local symptoms, %			
Pain	15	6	0.5
Swelling	2	0	>0.9
Erythema	1	0	>0.9
Moderate/severe systemic symptoms, %			
Fatigue	21	17	>0.9
Headache	9	12	>0.9
Myalgias	6	0	0.6
Chills	5	6	0.6
Fever	3	0	>0.9
Diarrhea	2	0	>0.9
Vomiting	1	0	>0.9

* N = 568, non-belatacept; N = 24, belatacept

** N = 381, non-belatacept; N = 19, belatacept