KI REPORTS
KIReports.org

Factors Associated With Reduced Anti-SARS-CoV-2 Antibody Responses After mRNA Vaccination in Kidney Transplant Recipients on Belatacept

Leela Morena[1,4], Ayman Al Jurdi[1,4], Jamil Azzi[2], Jay Fishman[1,3] and Leonardo V. Riella[1,3]

[1]Department of Surgery, Center for Transplantation Sciences, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA; [2]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; and [3]Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA

Correspondence: Leonardo V. Riella, Center for Transplantation Sciences, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street WHT 546, Boston, Massachusetts, 02114 USA. E-mail: lriella@mgh.harvard.edu

[4]LM and AAJ are co-first authors.

Received 10 April 2022; revised 6 July 2022; accepted 1 August 2022

Kidney Int Rep (2022) ■, ■–■; https://doi.org/10.1016/j.ekir.2022.08.001
KEYWORDS: COVID-19; kidney; transplantation; vaccine

INTRODUCTION

Belatacept is a costimulation blocker used for maintenance immunosuppression in kidney transplant recipients (KTRs) as an alternative to calcineurin inhibitors.[1] Studies evaluating SARS-CoV-2 vaccine responses in KTRs have shown reduced antibody responses in KTRs on belatacept.[2–4] Nevertheless, many of these studies included only a small number of patients on belatacept,[5] and had low rates of seroconversion, limiting the ability to evaluate factors associated with the development of antibody responses.[3,4] As a result, factors associated with lower odds of developing antibody responses in KTRs on belatacept are not known.

To address this gap, we conducted a retrospective multicenter cohort study of all KTRs on belatacept who received 3 homologous mRNA vaccine doses at Massachusetts General Hospital and Brigham and Women's Hospital. Per the institutions' policies, all KTRs on belatacept had anti-SARS-CoV-2 receptor-binding domain (RBD) antibodies measured by the Roche Elecsys immunoassay (≥0.80 U/ml defined as a positive result). KTRs who were not on belatacept for all 3 vaccinations, who had received different types of SARS-CoV-2 vaccines, or who had received anti-SARS-CoV-2 monoclonal antibodies for treatment or pre-exposure prophylaxis prior to antibody measurement were excluded. The primary outcome was the development of anti-RBD antibodies after the third vaccination. Secondary outcomes included factors associated with lower odds of developing anti-RBD antibody responses and the development of breakthrough infections. GraphPad Prism v9.1.2 (San Diego, CA) and SPSS v24 (Chicago, IL) were used for statistical analysis. This study was approved by Mass General Brigham's institutional review board (protocol:2019P002526).

RESULTS

From 159 KTRs reviewed, 58 met the inclusion criteria for the study (Supplementary Figure S1). Baseline characteristics for belatacept-treated KTRs who met inclusion criteria and those who did not are shown in Table 1 and Supplemantary Table S1, respectively. For KTRs on belatacept who met the inclusion criteria, the median age was 62 years (interquartile range [IQR] 51–66) and 69% were female. For induction immunosuppression, 72% received antithymocyte globulin, 21% received basiliximab, and 2% received alemtuzumab. For maintenance immunosuppression, 78% were on prednisone (median dose 5 mg, IQR 5–5 mg), 60% on mycophenolate (median total daily dose 1000 mg, IQR 750–1,000 mg), 9% on azathioprine, 9% on everolimus, 5% on tacrolimus, and 2% on sirolimus. Of those included in the study, 7% had SARS-CoV-2 infection prevaccination, 91% received BNT162b2 vaccine and 9% received mRNA-1273 vaccine. The median estimated glomerular filtration rate at the third vaccination was 50 ml/min per 1.73 m^2 (IQR 37–61). The median time from

Table 1. Baseline characteristics of kidney transplant recipients on belatacept

Characteristics	KTRs on belatacept (n = 58)
Age in yr, median (IQR)	62 (51–66)
Female, *n* (%)	40 (69)
Living donor transplant, *n* (%)	32 (55)
Yr from KT to first vaccine, median (IQR)	3.0 (2.2–5.6)
eGFR at third vaccine dose in ml/min/1.73 m^2, median (IQR)	50 (37–61)
Induction immunosuppression, *n* (%)	
Antithymocyte globulin	42 (72)
Basiliximab	12 (21)
Alemtuzumab	1 (2)
Data not available	3 (5)
Maintenance immunosuppression, *n* (%)	
Belatacept monotherapy	4 (7)
Prednisone	45 (78)
Median total daily dose in mg (IQR)	5 (5–5)
Mycophenolate	35 (60)
Median total daily dose in mg (IQR)	1000 (750–1000)
Azathioprine	5 (9)
Everolimus	5 (9)
Sirolimus	1 (2)
Tacrolimus	3 (5)
Months from KT to belatacept to KT, median (IQR)	6.0 (1.1–39.2)
History of allograft rejection, *n* (%)	12 (21)
Yr from last rejection to the first vaccine dose, median (IQR)	1.6 (0.9–2.2)
History of COVID-19 prior to first vaccine, *n* (%)	4 (7)
Type of vaccine received, *n* (%)	
BNT162b2	53 (91)
mRNA-1273	5 (9)
Months between second and third vaccines, median (IQR)	6.0 (6.1–7.6)
Months between third vaccine and anti-RBD antibody measurement, median (IQR)	5.0 (3.3–5.4)

eGFR, estimated glomerular filtration rate; IQR, interquartile range; KT, kidney transplantation; RBD, receptor-binding domain.

transplantation to belatacept conversion was 6 months (IQR 1.1–39.2). The median time from transplantation to the first vaccine was 3 years (IQR 2.2–5.6), from the second to the third vaccine was 6 months (IQR 6.1–7.6), and from the third vaccine to antibody measurement was 5 months (IQR 3.3–5.4). Twelve KTRs (21%) had a history of rejection at a median of 1.6 years (IQR 0.9–2.2) before the first vaccine dose. Details of rejection events and their treatment are summarized in Supplementary Table S2.

After the third vaccine, 32 of 58 KTRs on belatacept (55%) developed anti-RBD antibodies (Figure 1a). The median level of anti-RBD antibodies was 3.3 U/ml (IQR 0.0–344.8). When stratified by SARS-CoV-2 infection history (prevaccination or breakthrough), KTRs with SARS-CoV-2 infection before antibody measurement had higher antibody levels (median 66.6 U/ml, IQR 3.3–678.5) compared to KTRs who did not have SARS-CoV-2 infection before antibody measurement (median 0.0 U/ml, IQR 0.0–252.0, $P = 0.011$, Figure 1b). Using univariable logistic regression, we evaluated the association between patient, transplant, and vaccine characteristics with the odds of developing anti-RBD responses after vaccination. We found that age ≥60 years, estimated glomerular filtration rate <45ml/min per 1.73 m^2, prednisone use, and no history of SARS-CoV-2 infection were associated with significantly lower odds of developing anti-RBD responses after vaccination (Figure 1c). These associations between age, estimated glomerular filtration rate, and prednisone use remained significant in the multivariable logistic regression model adjusted for history of prior SARS-CoV-2 infection (Figure 1d). Because some centers recommend delaying vaccination after belatacept infusion in order to optimize antiviral responses,[4] we also evaluated the correlation between anti-RBD antibody levels and the number of days between vaccination and the most recent belatacept infusion for each vaccination but did not find an association between the 2 factors (Figure 1e–g).

At a median of 6 months (IQR 6.1–7.6) between the second and third vaccines, 4 patients (7%) developed a breakthrough infection after the second dose, 1 of whom required hospitalization (Supplementary Table S3). At a median follow-up of 3 months (IQR 2.4–3.1) after the third vaccine, breakthrough infection occurred in 9 KTRs (16%) after the third dose, 2 of whom required hospitalization. There were no deaths due to SARS-CoV-2 infection.

DISCUSSION

In summary, we report anti-RBD antibody responses after 3 doses of SARS-CoV-2 mRNA vaccines in KTRs on belatacept with a detailed evaluation of factors associated with developing antiviral antibody responses. Compared to the study by Chavarot *et al.*,[3] which found 6.4% antibody response after 3 vaccine doses in KTRs on belatacept, we found that 55% of KTRs on belatacept developed anti-RBD antibody responses. A possible explanation for this difference would be the improved responses observed in people with prior SARS-CoV-2 infection; this only accounts for a minority of our patients, given that 44% of infection-naïve KTRs developed anti-RBD antibodies. It is important to note that because prior COVID-19 status was confirmed by positive previous polymerase chain reaction, antigen, or antinucleocapsid antibody testing, and given that antinucleocapsid antibodies were not measured in all included KTRs, it is possible that some KTRs with asymptomatic prior infection could have been misclassified as infection-naïve in this analysis. Nevertheless, this is unlikely to have been the case in a significant proportion of our cohort, given the large

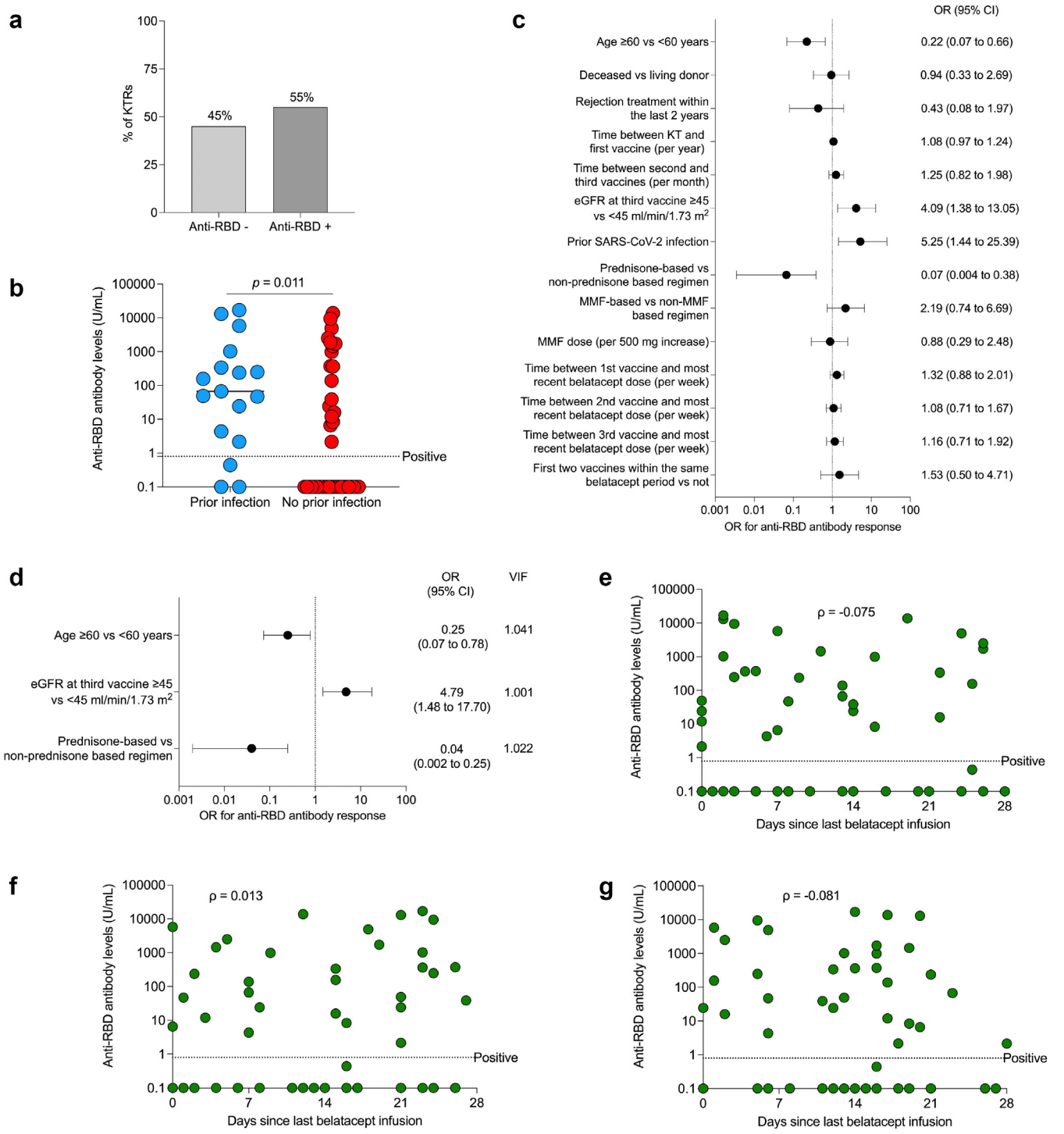

Figure 1. Anti-RBD antibody responses in kidney transplant recipients on belatacept after 3 doses of SARS-CoV-2 mRNA vaccination. (a) Percentage of KTRs on belatacept with and without anti-RBD antibody responses after 3 doses of SARS-CoV-2 of mRNA vaccines ($n = 58$). (b) Total (IgG + IgM + IgA) anti-RBD antibody levels measured by the Roche Elecsys immunoassay in KTRs with ($n = 17$) and without ($n = 41$) a prior history of SARS-CoV-2 infection. Horizontal line indicates positivity threshold of ≥0.80 U/ml. (c) Univariable logistic regression analysis of factors associated with the odds of developing an anti-RBD antibody response ($n = 58$). (d) Multivariable logistic regression analysis of factors associated with the odds of developing an anti-RBD antibody response adjusted for history of prior SARS-CoV-2 infection ($n = 58$). (e–g) Association between anti-RBD antibody levels and days between the most recent belatacept infusion and the (e) first, (f) second, and (g) third vaccines ($n = 57$). (b) Statistic by Mann-Whitney U test. (e–g) Statistic by Spearman's correlation. KT, kidney transplantation; MMF, mycophenolate mofetil; OR, odds ratio; RBD, receptor binding domain; VIF, variance inflation factor.

difference observed in anti-RBD responses between those classified as with versus those without prior COVID-19 in our cohort.

A possible explanation for a large proportion of the difference is that only 78% of KTRs in our cohort were on prednisone, compared to 100% in the study by Chavarot *et al*.[3] Prednisone use was strongly associated with a lower likelihood of anti-RBD responses in our study with only 27% of infection-naïve KTRs on prednisone developing anti-RBD antibodies versus 91% of those not on prednisone. Furthermore, our KTRs on prednisone were on lower doses (median 5 mg, IQR 5–5 mg) compared to Chavarot *et al*. (median 7.5 mg, IQR 5–10 mg).[3]

The limitations of our study include its small sample size, lack of a matched control group of KTRs on non-belatacept immunosuppression regimens, and its observational nature, which makes associations between exposure and outcome variables susceptible to confounding. Assessment of cellular immunity in such patients would also be informative.

In sum, our study adds to the literature by identifying prednisone use, age ≥60 years, estimated glomerular filtration rate <45ml/min per 1.73 m^2, and no history of SARS-CoV-2 infection as risk factors associated with the lack of development of anti-RBD antibodies after vaccination in KTRs on belatacept. It also shows that delaying vaccination after belatacept is not associated with improved antibody responses after vaccination. Additional strategies in this high-risk group are needed to improve vaccine responses and reduce risk of breakthrough infections.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

The study was funded in part by the Harold and Ellen Danser Endowed/Distinguished Chair in Transplantation at Massachusetts General Hospital (Boston, MA, USA).

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Subject inclusion flow diagram.

Table S1. Baseline characteristics of included and excluded kidney transplant recipients on belatacept.

Table S2. Prior allograft rejection events in kidney transplant recipients on belatacept.

Table S3. SARS-CoV-2 infections prior to antireceptor binding domain antibody measurement in kidney transplant recipients on belatacept.

REFERENCES

1. Vincenti F, Rostaing L, Grinyo J, et al. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med*. 2016;37:333–343. https://doi.org/10.1056/NEJMoa1506027
2. Chavarot N, Ouedrani A, Marion O, et al. Poor anti-SARS-CoV-2 humoral and T-cell responses after 2 injections of mRNA vaccine in kidney transplant recipients treated with belatacept. *Transplantation*. 2021;105:e94–e95. https://doi.org/10.1097/TP.0000000000003784
3. Chavarot N, Morel A, Leruez-Ville M, et al. Weak antibody response to three doses of mRNA vaccine in kidney transplant recipients treated with belatacept. *Am J Transplant*. 2021;21:4043–4051. https://doi.org/10.1111/ajt.16814
4. Noble J, Langello A, Bouchut W, Lupo J, Lombardo D, Rostaing L. Immune response post-SARS-CoV-2 mRNA vaccination in kidney transplant recipients receiving belatacept. *Transplantation*. 2021;105:e259–e260. https://doi.org/10.1097/TP.0000000000003923
5. Al Jurdi A, Gassen RB, Borges TJ, et al. Non-invasive monitoring for rejection in kidney transplant recipients after SARS-CoV-2 mRNA vaccination. *Front Immunol*. 2022;13:838985. https://doi.org/10.3389/fimmu.2022.838985