Humoral and Cellular Immune Response to a Third Dose of SARS-CoV-2 Vaccine in Kidney Transplant Recipients Taking Belatacept

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Kidney transplant recipients (KTRs) have poor humoral immune responses to 2-dose severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination, with noted improvement after receiving a third dose (D3).[1,2] However, KTRs taking belatacept (KTR-bela) have a worse humoral response to 2-dose SARS-CoV-2 vaccination[3] with minimal improvement after D3.[4] However, the cellular response after D3 in KTR-bela has not been well defined and could provide some protection against coronavirus disease 2019 infection. The goal of this study was to characterize the impact of a third vaccine dose on the humoral and cellular immune responses in KTR-bela compared with KTRs not taking belatacept (KTR-controls).

Twenty-five KTR-bela and 26 KTR-controls without previously diagnosed SARS-CoV-2 infection, who received 3 doses of SARS-CoV-2 vaccine, were identified from a previously described observational cohort.[1] Semiquantitative antispike serological testing was performed using the Roche Elecsys anti–SARS-CoV-2 S enzyme immunoassay, which tests for the receptor-binding domain, or the EUROIMMUN enzyme immunoassay, which tests for the S1 domain of the SARS-CoV-2 spike protein, at least 1 mo after dose 2 and repeated 2 to 4 wk after D3. Angiotensin-converting enzyme 2 (ACE2) inhibition (surrogate neutralization) of the vaccine strain and delta variant was measured using ACE2 MSD V-PLEX SARS-CoV-2 kits. This assay measures the ability of plasma to inhibit ACE2 binding to spike protein, and results are reported as percentage ACE2 inhibition. T-cell response was assessed using interferon-γ ELISpot assays as previously described.[5] A result was considered positive with spot-forming units of >20 per million peripheral blood mononuclear cells and a stimulation index of >3. This study was approved by the Johns Hopkins Institutional Review Board, and participants provided informed consent electronically.

The KTR-bela group had substantially lower antispike seroconversion than KTR-controls after D3 (any positive: 36% versus 76.9%; high positive: 16% versus 61.5%; $P = 0.003$) despite similar demographics, clinical factors, and vaccines administered (Table 1). There were differences noted in percentage ACE2 inhibition versus the vaccine strain (median [interquartile range], 5.2 [2.8–6.5] versus 13.3 [8.6–23.9]; $P < 0.01$) as well as the delta variant (median [interquartile range], 5.0 [3.1–8.4] versus 11.9 [3.3–15.7]; $P = 0.11$). All tested KTR-bela had results below

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TABLE 1.

Antibody response after 3 doses of SARS-CoV-2 vaccine in KTR-bela and KTR-control

Factor	KTR-bela	KTR-control	*P*
N	25	26	
Age, median (IQR)	61.9 (52.4–68.6) (n = 25)	59.7 (46.3–68.5) (n = 26)	0.78
Female	17 (68.0%)	14 (53.8%)	0.39
Non-White race	2 (8.0%)	0 (0.0%)	0.24
Time since transplant, median (IQR)	3.4 (2.1–8.8) (n = 25)	6.1 (2.1–12.6) (n = 26)	0.40
MMF	17 (68.0%)	21 (80.8%)	0.35
D2 vaccine type			0.58
BNT162b2	13 (52.0%)	16 (61.5%)	
mRNA-1273	12 (48.0%)	10 (38.5%)	
D3 vaccine type			0.26
BNT162b2	9 (%)	8 (%)	
mRNA-1273	13 (%)	10 (%)	
Ad26.COV2.S	3 (%)	8 (%)	
Pre-D3 antibody response[a]			0.50
Negative	20 (80.0%)	19 (73.1%)	
Low positive	4 (16.0%)	7 (26.9%)	
High positive	1 (4.0%)	0 (0.0%)	
Post-D3 antibody response[a]			0.003
Negative	16 (64.0%)	6 (23.1%)	
Low positive	5 (20.0%)	4 (15.4%)	
High positive	4 (16.0%)	16 (61.5%)	
% ACE2 inhibition, median (IQR)			
Vaccine strain	5.2 (2.8–6.5) (n = 5)	13.3 (8.6– 23.9) (n = 26)	0.008
Delta variant	5.0 (3.1–8.4) (n = 5)	11.9 (3.3–15.7) (n = 26)	0.11

[a]Negative—anti-RBD <50 U/mL or anti-S1 <1.1 AU/mL; low positive—anti-RBD ≥50 U/mL but <250 U/mL or anti-S1 ≥1.1 AU/mL but <4 AU/mL; high positive—anti-RBD ≥250 U/mL or anti-S1 ≥4 AU/mL.

ACE2, angiotensin-converting enzyme 2; D2, dose 2; D3, dose 3; IQR, interquartile range; KTR-bela, kidney transplant recipients taking belatacept; KTR-control, kidney transplant recipients not taking belatacept; MMF, mycophenolate mofetil; RBD, receptor-binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

a level consistent with detectable neutralizing antibody[2] and failed to meet criteria for a positive ELISpot (3 of 3).

Our findings of low seroconversion after D3 in KTR-bela are consistent with a recent report from Chavarot et al[4] and extend their study by providing a similar control group receiving nonbelatacept immunosuppression. In addition, differences seen between the 2 groups in percentage ACE2 inhibition highlight the diminished potential for virus neutralization and the risks posed by novel SARS-CoV-2 variants. Most importantly, our study is the first to highlight the lack of cellular immune response to an additional vaccine dose in KTR-bela. Limitations include a lack of safety information, lack of vaccine-specific T-cell response testing, and small sample size.

These findings suggest minimal potential benefit to the cellular immune response and virus neutralization potential after D3 in KTR-bela. Investigation of alternative methods, such as preexposure monoclonal antibody prophylaxis, is necessary to improve protection against coronavirus disease 2019 in this particularly vulnerable group.

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