Impaired Humoral and Cellular Responses to COVID-19 Vaccine in Heart and Lung Transplant Recipients

To the Editor:

Solid organ transplant recipients are at high risk from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with reported mortality rates of up to 39%, with emerging data demonstrating impaired humoral responses to vaccination (1, 2). Sparse data exist examining T-cell immunity (3–6). The calcineurin inhibitors, tacrolimus and cyclosporin, specifically inhibit T-cell activity. We hypothesized that highly immunosuppressed cardiothoracic transplant recipients (HICTTR) on triple immunosuppression are at an immunological disadvantage and are unlikely to produce robust humoral or cellular immune responses to the SARS-CoV-2 vaccination.

Methods

Study population. The study population consisted of two cohorts, SARS-CoV-2 infection–naive healthcare workers (HCW) ($n = 69$) and HICTTR ($n = 58$). Inclusion criteria: vaccination for SARS-CoV-2 with two doses of either BNT162b2 or the ChAdOx1 vaccine and HICTTR on immunosuppression with a calcineurin inhibitor, an antiproliferative agent, and corticosteroids. Both cohorts underwent paired analysis of serological and cellular response to SARS-CoV-2 vaccination. Past infection was defined as a positive PCR or a positive antinucleoprotein test result at any time or a positive antispike protein (S) and/or reactive T-cell enzyme-linked immunospot assay (ELISpot) before vaccination. Study participants were recruited into two nationally approved studies evaluating immune responses after SARS-CoV-2 vaccination in HCW and HICTTR. All individuals gave informed consent (references: 20/SC/0208 and 20/WA/0123). Some of the HCW data used in the study have been previously published (5).

Serological testing. Serum was tested for antibodies to nucleocapsid protein (antinucleoprotein), a marker of recent SARS-COV-2 infection, using the Abbott Architect SARS-CoV-2 IgG two-step chemiluminescent immunoassay. Antibodies to the receptor-binding domain of spike protein (anti-S IgG) were detected using the Abbott Architect SARS-CoV-2 IgG Quant II chemiluminescent immunoassay (5). The threshold for a positive antibody response was an anti-S antibody concentration of more than 7.1 binding antibody units (BAU)/ml. Neutralizing antibody concentrations were not measured.

T-cell ELISpot. SARS-CoV-2 specific T-cell responses were detected using the T-SPOT Discovery SARS-CoV-2 (Oxford Immunotec), which includes S1 and S2 SARS-CoV-2 peptide pools according to the manufacturer's instructions (5). The threshold for a positive T-cell immune response was set as the mean and three standard deviations of interferon-γ spot counts (>40 spot-forming units/10^6 peripheral blood mononuclear cells) (7).

Statistical analysis. Continuous variables are presented as the median and interquartile range, and categorical variables as count and percentage. The chi-square/Fisher's exact test or the Mann-Whitney test were used for categorical or continuous variables, respectively. Multivariable analysis was done with multiple logistic regression for HICTTR. Statistical analysis was conducted using IBM SPPS Statistics version 27.

Results

Fifty-nine (85%) HCW and 27 (47%) HICTTR subjects received the BNT162b2 vaccine; 10 (15%) HCW and 31 (53%) HICTTR subjects received the ChAdOx1 vaccine. The median vaccine dosing interval in days was 68 (62–71) and 77 (70–79) for the HCW and HICCTR cohorts, respectively. The median time to sampling in days after vaccination was 28 (21–28) and 77 (70–89) for the HCW and HICCTR cohorts. The median number of months from transplantation to the first vaccine dose was 64 (32–99). Demographic data and details of immunosuppressive regimens are presented in Table 1.

Serological response after vaccination. All HCW seroconverted with higher median anti-S concentrations for BNT162b2 (1,176 [651–2554]) and ChAdOx1 (256 [78–723]), respectively ($P = 0.001$). Seroconversion was observed in 15/58 (26%) HICCTR subjects. BTN162b (12/27 [44%]) vaccine recipients were more likely to seroconvert than ChAdOx1 vaccine recipients (3/31 [10%]; $P = 0.03$) (Figure 1 and Table 1). Median anti-S concentrations were significantly lower in HICTTR than HCW for both vaccines (Table 1). There was no significant difference in anti-S levels in HICCTR subjects who received BNT162b compared with ChAdOx1 ($P = 0.183$) (Table 1). Immunosuppressive regimens did not differ by vaccine group (Table 1) and serum calcineurin inhibitor concentrations over the preceding 3 months in HICTTR vaccine recipients who seroconverted were 7.2 ng/ml (6.2–8.6), similar to those who did not (7.6 ng/ml [6.6–8.5]; $P = 0.72$).

Univariate analysis identified the ChAdOx1 vaccine, higher creatinine, and low estimated glomerular filtration rate as predictors of failure to seroconvert. In the final model, after adjusting for age, vaccination with the BNT162b2 vaccine was independently associated with an increased likelihood of seroconversion (Beta 8.6; 95% confidence interval, 1.9–38.7; $P = 0.005$).

Cellular immune responses. T-cell immune responses to SARS-CoV-2 peptides were detected in 91% of HCW subjects compared with 21% of HICTTR subjects ($P < 0.0001$) (Table 1). There were no differences in the proportion of T-cell response to the vaccine in both study cohorts. T-cell immune responses and anti-S antibodies were detected in 54/59 (92%) of HCW and 4/58 (7%) of HICTTR vaccine recipients.

Discussion

This study examined the immunogenicity of two doses of SARS-CoV-2 vaccines in infection-naive HICTTR and showed

Supported by donations from the Harefield Transplant Club and individual donations from patients. A.S. is supported by a Medical Research Council Clinical Academic Research Partnership award (MR/TOO5572/1) and by the MRC center grant MR/R015600/1.

Originally Published in Press as DOI: 10.1164/rccm.202109-2026LE on March 25, 2022

Table 1. Baseline Clinical Characteristics, Serological and T-Cell Responses after SARS-CoV-2 Vaccination in 58 Infection-Naive Highly Immunosuppressed Cardiothoracic Transplant Recipients and 69 Naive Healthcare Workers

	Cohort 1, HCW (*n* = 69)	Cohort 2, HICTTR (*n* = 58)	*P* Value*
Sex, *n* (%)			
Male	24 (35)	29 (50)	0.07
Female	45 (65)	29 (50)	—
Age, yr (median, IQR)	42 (33–52) (n:68	52 (40–58)	<0.0001)
Transplant indication, *n* (%)			
CF/bronchiectasis	—	21 (36)	—
COPD	—	14 (24)	—
ILD	—	10 (17)	—
PAH	—	4 (7)	—
Cardiomyopathy	—	4 (7)	—
Other	—	5 (8)	—
Vaccine type, *n* (%)			
BNT1262b2	59 (85)	27 (47)	<0.0001
ChAdOx1	10 (15)	31 (53)	—
Seroconversion, *n* (%)			
Both vaccines	68/68 (100)†	15/58 (26)	<0.0001
Seroconversion according to vaccine type, *n* (%)			
BNT1262b2	58/58 (100)	12/27 (44)	<0.0001
ChAdOx1	10/10 (100)	3/31 (10)	<0.0001
Serology level according to vaccine type (BAU/ml) (median, IQR)			
BNT1262b2	1176 (651–2554)	2.28 (0.34–78.09)	<0.0001
ChAdOx1	256 (78–723)	0.56 (0.44–1.15)	<0.0001
Positive T-cell response, *n* (%)			
Both vaccines	61/67 (91)†	12/58 (21)	<0.0001
Positive T-cell response according to vaccine type, *n* (%)			
BNT1262b2	52/58 (91)	5/27 (19)	<0.0001
ChAdOx1	9/9 (100)	7/31 (23)	<0.0001
T-cell level according to vaccine type (SFU/10^6 PBMC) (median, IQR)			
BNT1262b2	190 (91–282)	12 (4–28)	<0.0001
ChAdOx1	160 (130–274)	16 (4–32)	<0.0001

Definition of abbreviations: BAU = binding antibody units; CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; HCW = healthcare workers; HICTTR = highly immunosuppressed cardiothoracic transplant recipients; ILD = interstitial lung disease; IQR = interquartile range; PAH = pulmonary arterial hypertension; PBMC = peripheral blood mononuclear cells; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SFU = spot forming units.
Immunosuppression was comparable as per the inclusion criteria. The median prednisolone dose was 10 mg/d (5–10) (median, IQR), the dose for mycophenolate mofetil was 1 g/d (1–1) (median, IQR), and the tacrolimus dose was 4.75 mg/d (3–7.5) (median, IQR). There was no significant difference between serum calcineurin inhibitor concentrations over the preceding 3 months in HICTTR subjects who seroconverted versus those who didn't: 7.2 ng/ml (6.2–8.6) (median, IQR) and 7.6 ng/ml (6.6–8.5) (median, IQR), respectively; $P = 0.72$. HCW subjects are believed not to have significant morbidity (individuals not requiring occupational health clearance to work from home and/or be redeployed from patient-facing roles due to significant comorbidities that would increase their risk of complications from SARS-CoV-2 infection).
*Comparison between HCW and HICTTR.

that immunogenicity is poor, with low seroconversion rates (26%) and low rates of detectable T-cell responses (21%). Only 7% developed evidence of both humoral and T-cell responses following vaccination. The median serum concentrations of anti-S IgG in HICTTR are significantly lower than in vaccinated HCW, raising the concern that even those with detectable antibody concentrations may not have the same degree of protection from severe disease.

Analysis according to vaccine type showed that only 10% of subjects who received CHAdOx1 had detectable S antibody levels. The BNT162b2 vaccination induced significantly greater anti-S IgG responses (44%). Our findings are lower than reported in a renal transplant cohort (5, 8) and can be explained by more intensive immunosuppressive regimens used in this study. T-cell responses in this study were attenuated following both BNT162b2 and ChAdOx1 vaccination but were comparable to those detected in renal transplant vaccine recipients.

Clinical implication. Although we report vaccine biomarkers and not clinical outcomes, our results raise significant concerns about the degree of protection provided against severe coronavirus disease (COVID-19) infection disease after vaccination in this population.

Limitations. Study limitations include small sample size, age disparity, the difference in time between vaccination doses and sampling between control and transplant cohorts, and limited immunogenicity outputs. Neutralizing antibodies were not measured, and the collection of clinical outcome data was beyond the scope of this small study. Further work to comprehensively define vaccine immunogenicity and efficacy after booster dosing is urgently required in this cohort.

Conclusions

This study confirms attenuated humoral and cellular responses to BNT162b2 and ChAdOx1 vaccination in HICTTR. Data are urgently needed on vaccine efficacy against newer SARS-CoV-2

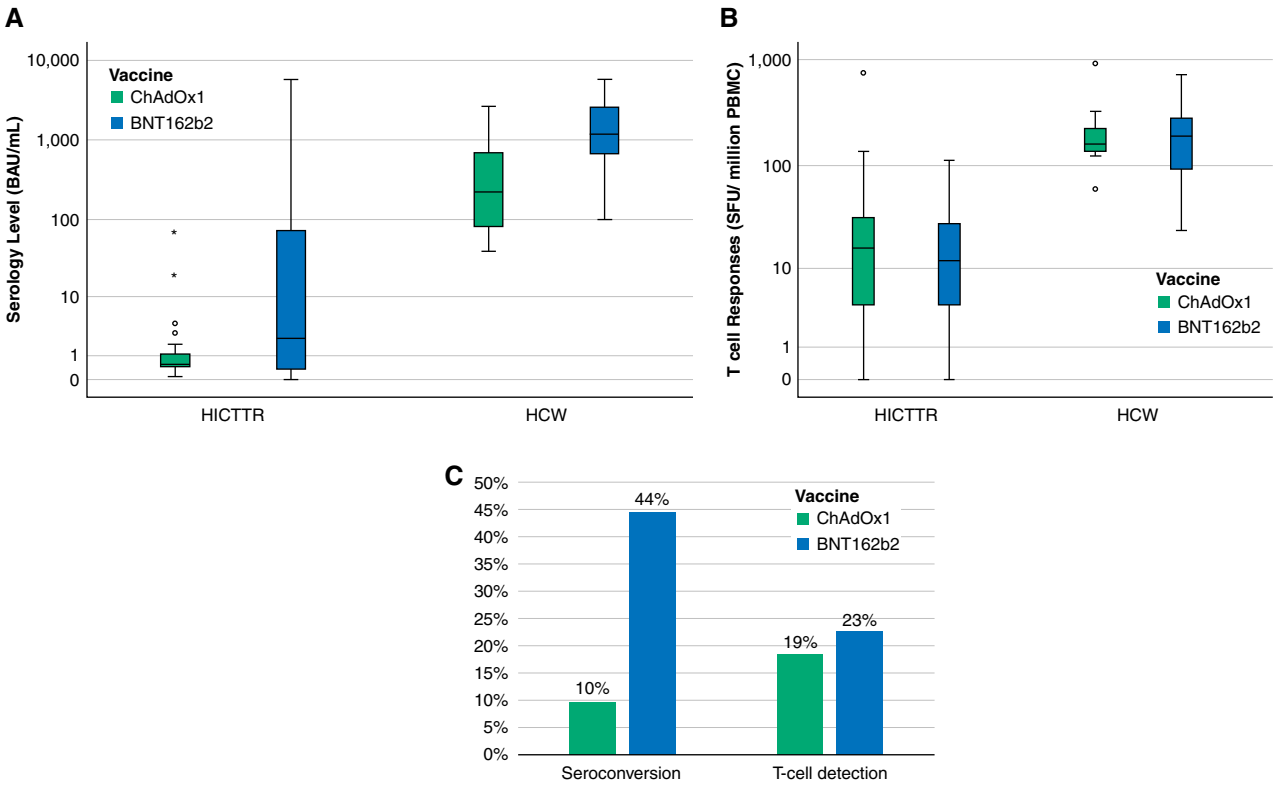

Figure 1. (*A*) Serological response after vaccination (BAU/ml) in 58 cardiothoracic transplant recipients and 68 naive healthcare workers (HCW) according to vaccine type. Highly immunosuppressed cardiothoracic transplant recipients (HICTTR) had significantly lower serology levels ($P < 0.0001$). Asterisks indicate outliers. (*B*) T-cell levels following vaccination (peripheral blood mononuclear cells per million) in 58 HICTTR and 67 HCW according to vaccine type. HICTTR had significantly lower T-cell concentrations ($P < 0.0001$). (*C*) Seroconversion rate and T-cell response in 58 HICTTR subjects following vaccination according to vaccine type. Vaccination with the BNT162b2 vaccine resulted in a significantly higher probability of seroconversion than the ChAdOx1 vaccine (12/27 [44%] and 3/31 [10%], respectively; $P = 0.003$). There was no difference in the T-cell detection rate after vaccination with the BNT162b2 compared with the ChAdOx1 vaccine (5/27 [19%] and 7/31 [23%], respectively; $P = 0.58$). For *A* and *B*, values have been log-transformed. BAU = binding antibody units; PBMC = peripheral blood mononuclear cells; SFU = spot forming units.

variants capable of evading preexisting immune responses in larger HICTTR cohorts. In the interim, vaccination of household contacts and children and adherence to nonpharmaceutical interventions are recommended for this vulnerable patient cohort. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

Acknowledgment: The authors thank the following individuals, without whom this work would not have been possible: Dr. Darius Armstrong-James, Sophia Crasto, Michelle Parker, and our Harefield research nurses and cardiology colleagues. The authors also thank Jaid Debrah, Alison Cox, and the patient charity group (Harefield Transplant Club).

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Continuous Positive Airway Pressure for Cognition in Sleep Apnea and Mild Cognitive Impairment: A Pilot Randomized Crossover Clinical Trial

To the Editor:

Obstructive sleep apnea (OSA) is estimated to occur in up to 1 billion adults worldwide (1). The importance of OSA in individuals with mild cognitive impairment (MCI) is becoming increasingly recognized (2). Accumulating evidence suggests that OSA is associated with an increased risk for cognitive decline and dementia (3). However, it remains unclear if treating OSA in at-risk individuals has positive cognitive benefits. Here we present a pilot randomized controlled crossover study that investigated 12 weeks of continuous positive airway pressure (CPAP) treatment on cognition compared with no treatment in older adults with clinical MCI and OSA. Outcome assessors were blinded to treatment allocation. This study was approved by the University of Sydney Ethics review committee (2012/2877) and was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12614000442606). All participants provided informed consent before any study assessments.

Participants who met clinical criteria for MCI (4) were recruited from the Healthy Brain Ageing Clinic, Sydney, New South Wales, Australia. Eligible participants were adults aged 50–80 years, with at least moderate OSA as defined by an apnea–hypopnea index (AHI) $\geq$ 15 events/h (using 4% O_2 desaturation for events) by overnight in-laboratory (Woolcock Institute of Medical Research) polysomnography. Participants had a CPAP initiation, mask fitting, and short acclimatization with a CPAP therapist before their in-laboratory CPAP pressure determination study, except one participant who underwent a home titration. After commencing CPAP, follow-up was with a CPAP therapist at 1 and 4 weeks with *ad hoc* follow-up phone and/or face-to-face contact when required. Participants in the no-treatment arm were contacted every 4 weeks.

A computer-generated randomization list (1:1 ratio) was created and held on a password-protected system by investigators who never had any patient contact. Randomization was stratified by OSA severity (AHI $>$ 30 events/h). Secure randomization was achieved by only releasing allocation until after the participants' unique screening number, date of birth, and AHI were irrevocably provided. Blinding was maintained by asking participants not to disclose their treatment allocation to any assessor, and the outcome assessors had no role in patient selection and treatment. Assessments were performed by trained

Supported by Dementia Australia Research Foundation grant DGP1300034, National Health and Medical Research Council (NHMRC)–Australian Research Council Dementia Research Development Fellowships GTN1104003 and 1107716 (C.M.H., A.L.D'R.), NHMRC Senior Principal Research Fellowship/Investigator grant GTN1106974/1197439 (R.R.G.), and NHMRC Dementia Leader Fellowship GTN1135639 (S.L.N.). C.M.H. is also funded by a National Heart Foundation Future Leader fellowship. ResMed was not involved in any aspect of the study, including design and data collection.

Originally Published in Press as DOI: 10.1164/rccm.202111-2646LE on May 18, 2022