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TRANSPLANT INFECTIOUS DISEASE

BRIEF COMMUNICATION

Humoral response to heterologous prime-booster vaccination in heart transplant recipients aged 18–70 years primed with a viral vector SARS-CoV-2 vaccine

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Abstract

Solid organ transplant recipients have demonstrated a blunted immune response to standard 2-dose vaccination against SARS-CoV-2. This study sought to determine the humoral response to heterologous booster vaccination (viral vector vaccine dose 1 and 2 + mRNA booster). Heart transplant recipients, aged 18 to 70 years of age who initially received two doses of the viral vector ChAdOx1 nCoV-19 vaccine followed by a BNT162b2 mRNA booster were recruited. A detectable antibody response in the absence of prior SARS-CoV-2 was the primary outcome measured. This was defined as an anti-spike titre of ≥0.8 U/mL on the Elecsys anti-SARS-CoV-2 S immunoassay. A total of 80 heart transplant patients (mean age 49 ± 13 years, 28% female) were included. Blood samples were drawn at a median of 30 (IQR 28-33) days after the BNT162b2 mRNA booster. The frequency of a detectable antibody response increased from 37.5% (n = 30) after dose 2 to 56% (n = 45) post dose 3 ($p < 0.001$). A non-detectable antibody response was significantly more common in recipients with a shorter time interval from transplantation ($p < 0.001$), lower likelihood of cardiac allograft vasculopathy (p = 0.003) and in those prescribed a triple versus dual immunosuppressant regime ($p = 0.009$) and a tacrolimus versus cyclosporine basedregimen ($p = 0.007$). Despite heterologous prime-booster vaccination 44% of this vulnerable population ultimately continue to have no detectable antibodies.

KEYWORDS
heart transplant, heterologous prime-booster vaccination, humoral response, SARS-CoV-2

Abbreviations: CKD, chronic kidney disease; mRNA, messenger ribonucleic acid; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus- 2; SOT, solid organ transplant.

1 | INTRODUCTION

Solid organ transplant (SOT) recipients are an inherently high-risk patient cohort with a disproportionately high risk of mortality from SARS-CoV-2 compared to the general population.[1,2]

Following an initial two-dose SARS-CoV-2 vaccination regimens, irrespective of vaccine subtype, SOT recipients have demonstrated an attenuated immune response compared to the general population.[3–5] A third dose mRNA vaccine following an initial two-dose mRNA strategy—"homologous booster"—was found to augment humoral immune response in some SOT recipients, but overall positive antibody responses remain suboptimal.[6,7] Heterologous prime-booster (viral vector vaccine as dose 1 and 2 followed by mRNA as 3rd dose) vaccination has demonstrated a greater immune response compared to homologous boosters in immunocompetent vaccine recipients.[8–10] Whether this finding translates to an immunosuppressed cohort such as SOT recipients is unknown.

This study sought to examine the safety and humoral response of a 3rd "booster" dose mRNA vaccine (BNT162b2) in heart transplant recipients aged 18–70 years initially treated initially with two doses of the ChAdOx1 nCoV-19(ADZ 1222) viral vector vaccine.

2 | MATERIALS AND METHODS

This prospective cohort study was undertaken at the National Heart and Lung Transplant Centre at the Mater University Hospital Dublin, Ireland. Heart transplant recipients aged 18–70 years of age without a history of SARS-CoV-2 infection who had received two initial doses of the ChAdOx1 nCoV-19(ADZ 1222) viral vector vaccine were eligible to participate. Each patient had a known antibody status after each of the initial two vaccines from phase one of our study.[5]

All patients provided written informed consent and completed a questionnaire that included assessment of any prior or interim (between dose 3 to blood sample) confirmed SARS-CoV-2 infection. Exclusion criteria included pregnancy, recent heart transplantation (30 days), and prior SARS-CoV-2 infection at any time leading up to study inclusion. A reaction to vaccination that led to a patient requiring seeking medical attention or hospital admission was defined as a serious adverse reaction. Donor-specific antibody levels were tested before the index SARS-CoV-2 vaccination.

Baseline demographic, clinical, and transplant-specific characteristics were compared among those who had a detectable antibody response after two doses of the vaccine and those who did not.

Ethical approval was granted by the Institutional Review Board at the Mater Misericordiae University Review Board (Ref: 1/378/2239).

2.1 | Vaccination schedule

The Irish National Immunization Advisory Committee directed that heart transplant recipients aged 18–70 years of age receive two doses of the ChAdOx1 nCoV-19 vaccine beginning in March 2021 with 2nd doses after a 12-week interval. Details of blood sampling and timing of initial antibody results have been published.[5] Extended primary vaccination with an mRNA-based vaccine ("booster") was recommended for immunocompromised individuals and was administered for heart transplant recipients between October and November 2021.

Blood samples were obtained to assess antibody response 4 weeks later. The median time interval between patient's the 2nd and 3rd vaccine was 3.7 (3.3, 4.1) months.

2.2 | Humoral response assessment

Blood samples were analyzed in an International Organizational for Standardization (ISO 15189) accredited laboratory. Each sample was tested for total antibodies (IgM and IgG) against the receptor binding domain of the spike (S) protein (anti-spike antibody) using the quantitative Elecsys anti-SARS-CoV-2 S electrochemiluminescence immunoassay (Roche Diagnostics, Germany). Demonstrable titres >250 U/ml were diluted 10-fold to provide a value up to 2500 U/ml (as is feasible according to manufacturer instructions). Internal and manufacturer evaluation of this assay confirmed a sensitivity and specificity of >97% for each test.[11]

Patient samples were also analyzed for antinucleocapsid antibodies using the qualitative Elecsys anti-SARS-CoV-2 (Roche Diagnostics, Germany) to complement patient questionnaires in excluding prior SARS-CoV-2 infection. Prior infection was identified by a validated index of ≥1.0.[11]

A detectable antibody response was the primary outcome of interest and defined as an antispike titre of ≥0.8 U/ml in the absence of prior laboratory confirmed SARS-CoV-2 infection.

2.3 | Statistical analysis

Statistical analyses for this study were performed using IBM SPSS Statistics 27. Categorical data are presented as frequencies and percentages. Continuous variables are presented as either mean ± standard deviation (SD) or median (Q1; Q3). For the analysis of two nominal datasets, a chi square test (X^2) or Fisher's exact test was used, while a Mann–Whitney *U* test was used for non-normally distributed data when comparing nominal and ordinal data.

3 | RESULTS

In total, 80 heart transplant recipients (mean age 49 ± 12.6 years, 28% female, median 7.7 [3.8, 14.4] years since transplantation) participated in this study. Patient characteristics compared between those both with and without a detectable antibody response are outlined in Table 1.

Blood samples for the cohort were drawn at a median of 30 (IQR 28–33) days after inoculation with the BNT162b2 mRNA booster. All included patients had a negative antinucleocapsid antibody result and

TABLE 1 Characteristics of the total population and divided according to a detectable and nondetectable antibody response

	Total $n = 80$	Nondetectable antibody response, $n = 35$	Detectable antibody response, $n = 45$	p-Value
Age (mean ± SD)	49.8 ± 12.6	52.7 ± 12.2	47.6 ± 12.6	.07
Female, *n* (%)	23 (28.4%)	12 (36%)	11 (24%)	.3
Years since heart transplantation, median (IQR)	7.7 (3.8, 14.4)	5 (3.4, 7.8)	9.9 (5.8, 18)	<.001
Graft function				
CAV/CAD, *n* (%)	20 (24.7%)	3 (8.6%)	17 (38%)	.003
EF > 50%, *n* (%)	76 (93.8%)	33 (94.3%)	43 (96%)	1
Hypertension, *n* (%)	65 (80%)	26 (74%)	39 (87%)	.16
CKD stage ≥3, *n* (%)	52 (64.2%)	27 (77%)	25 (55.6%)	.06
Diabetes, *n* (%)	15 (18.5%)	6 (17%)	9 (20%)	.7
Rejection history				
Acute cellular rejection ≥2R, *n* (%)	40 (49.4%)	21 (60%)	19 (42%)	.17
Antibody mediated rejection, *n* (%)	5 (6.2%)	3 (9%)	2 (4%)	.65
Donor-specific antibodies				
Negative, *n* (%)	54 (66.7%)	25 (71%)	29 (64%)	.5
Weak, *n* (%)	14 (17.3%)	7 (20%)	7 (16%)	
Significant, *n* (%)	8 (9.9%)	2 (6%)	6 (13%)	

Abbreviations: CAD, coronary artery disease; CAV, cardiac allograft vasculopathy; CKD, chronic kidney disease; EF, ejection fraction; SD, Standard deviation.

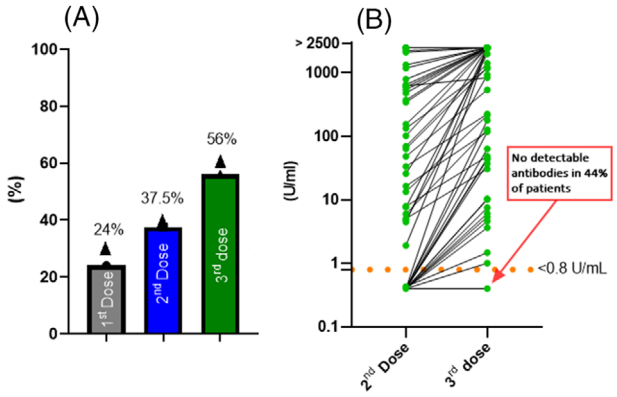

FIGURE 1 (A) Frequency of a detectable antibody response after each vaccination for 80 heart transplant recipients. (B) Interval change in anti-spike antibody titres between the 2nd ChAdOx1 nCoV-19 vaccine and the 3rd dose mRNA (BNT162b2) booster vaccine. *Note*: each ● frequency represents more than one person. Dotted line = threshold for detectable antibody response to SARS-C0V-2 vaccination (≥0.8 U/ml)

had no documented history of prior infection or known close contacts of a SARS-CoV-2 case for the duration of the study. Just over a third (37.5%, $n = 30$) of this study cohort had a positive antibody response to the two-dose ChAdOx1 nCoV-19 vaccine regimen, and this increased significantly after the 3rd dose to 56% ($n = 45$), $p < .001$ (Figure 1A). Among those with a positive antibody response to the third vaccine dose median antispike titres increased from 15 (0.4, 515) U/ml after the second dose to 941 (476, 6986) U/ml, Figure 1b. No patient had a serious adverse reaction to their booster vaccine.

Differences in clinical characteristic are shown in Table 1; a nondetectable antibody response was significantly associated with shorter time interval from transplantation ($p < .001$), lower likelihood of cardiac allograft vasculopathy ($p = .003$) and trended toward significantly more common in those with chronic kidney disease (CKD) stage ≥3 ($p = .06$). In addition, those with a nondetectable antibody response tended to be older, although this did not reach significance. No patient developed antibody mediated or ≥2R cellular rejection during the study period. Further, no differences were seen according to history of rejection or presence of donor-specific antibodies.

Table 2 illustrates differences between detectable and nondetectable antibody responses according to immunosuppressive regimens. Those with a nondetectable antibody response ($n = 35$) after the 3rd dose vaccination were more likely to be on a triple immunosuppressant regime ($n = 25$, 71%) compared to a dual immunosuppressant regime ($n = 10$, 29%), $p = .009$. Furthermore, those with a nondetectable antibody response were more likely prescribed a tacrolimus (versus cyclosporine)-based regimen ($p = .007$) and prednisolone ($p = .001$). A mycophenolate-including regimen trended toward being more common in those without a detectable antibody response (80% vs. 62%, $p = .08$).

4 | DISCUSSION

This study describes the first analysis of heterologous booster vaccination in heart transplant recipients initially treated with two doses of a replication-deficient adenoviral vector vaccine program. The study

TABLE 2 Immunosuppressant regimen of the total population and divided according to a detectable and nondetectable antibody response

	Total $n = 80$	Nondetectable antibody response, $n = 35$	Detectable antibody response, $n = 45$	p-Value
Number of immunosuppressants	2.6 ± 0.5	2.7 ± 0.5	2.4 ± 0.5	.01
Dual immunosuppressant therapy, *n* (%) Triple immunosuppressant therapy, *n* (%)	36 (45%) 44 (55%)	10 (28%) 25 (71%)	26 (58%) 19 (42%)	.009
Mycophenolate-based regimen, *n* (%)	56 (70%)	28 (80%)	28 (62%)	.08
Mycophenolate-based regimen dose (BD)	808 ± 309	759 ± 293	795 ± 305	.7
Azathioprine, *n* (%)	10 (13%)	3 (9%)	7 (16%)	.5
Cyclosporin, *n* (%)	13 (16%)	1 (3%)	12 (27%)	.007
Azathioprine dose (OD)	78 ± 49	108 ± 52	64 ± 45	.17
Tacrolimus, *n* (%)	68 (85%)	34 (97%)	34 (76%)	.007
Tacrolimus level	8 ± 2	8.8 ± 1.8	8.1 ± 2.2	.15
Prednisolone, *n* (%)	48 (60%)	28 (80%)	20 (44%)	.001
Prednisolone dose (OD)	5.8 ± 2	6.2 ± 2.3	5.2 ± 1.8	.1
Sirolimus, *n* (%)	9 (11.3%)	0	9 (20%)	N/A

Note: Values are expressed as mean ± standard deviation unless specified.
Abbreviations: BD, twice daily; OD, once daily; N/A, not applicable.

demonstrated: (1) use of this strategy in this patient group was safe; (2) the frequency of a detectable antibody response increased significantly from 37.5% to 56% ($n = 45$) after the mRNA (BNT162b2) booster was administered; (3) those with a persistent non-detectable response (44%) were more likely to have a shorter time interval since transplant and be prescribed more intensive immunosuppressive regimens.

Our findings are broadly similar to two recently published studies in SARS-CoV-2 naive SOT recipients, which used homologous 3rd dose or booster regimens—where antibody response increased from 23% to 67% in an Israeli heart transplant patient cohort ($n = 96$) and from 40% to 68% in a French mixed SOT patient group ($n = 101$).[6,7] Furthermore, a recent large meta-analysis reported a positive humoral response in 63.1% (49.1%–69.1%) of SOT recipients after a third mRNA Covid-19 vaccine.[12] Notably, despite a third vaccine, humoral response among SOT recipients remains significantly lower than the >99% detectable antibody response (threshold, >0.8 U/ml) achieved with two ChAdOx1 nCoV-19 vaccines, which has already been demonstrated among immunocompetent individuals.[13,14]

Heterologous versus homologous 3rd dose vaccinations were compared in a randomized clinical trial in a post-kidney transplant population.[15] In the 197 recipients who had been primed with two prior mRNA vaccines, no significant difference in antibody response was demonstrated between those given a 3rd dose vector vaccine or repeat mRNA-based vaccine.[15] This is in contrast to a recent observational study of 337 SOT recipients (10% heart) that compared a heterologous viral vector Ad.26.COV2.S booster to homologous mRNA booster in patients who were seronegative after two mRNA vaccines.[16] Those treated with a Ad.26.COV2.S booster were more likely (1.4 fold) to have a positive antibody response at 3 and 6 months after booster vaccination. However, this study is limited by the observational design and relatively small group ($n = 30$ at 3 months and $n = 17$ at 6 months) receiving heterologous vaccination.[16]

Studies in post-SOT recipients including those in heart transplant populations have also shown similar association between lower likelihood of detectable antibody response and certain patient characteristics, particularly those reflecting immunosuppression regimen intensity.[5,6] In our published two-vaccine dose study, the presence of chronic kidney diseas (CKD) and mycophenolate mofetil use was both found to be independently associated with a nondetectable response in a multivariate model, findings replicated in the study by Peled et al. in the Israeli cohort in association with postdose 3 results.[5,6] In the current study, a mycophenolate-based regimen was numerically more likely in those with a nondetectable antibody response compared to detectable (80% vs. 62%) but only trended toward significance ($p = .08$), likely reflecting the modestly smaller numbers completing this study. Furthermore, shorter time interval since transplant and triple versus dual immunosuppressant regimens were significantly more common in those with a nondetectable response; similar signals were seen in both the postkidney transplant population in the randomized clinical trial noted above and a recent meta-analysis on SOT recipients.[12] The association of these variables is in turn likely to explain the significant associations between tacrolimus (use more likely to reflect shorter time interval since transplant) and prednisolone containing-regimens (use more likely to occur as part of a triple drug regimen) and a nondetectable antibody response. Finally, the association between lower cardiac allograft vasculopathy (CAV) rates and a nondetectable antibody response is less likely indicative of a direct relationship between the presence or absence of CAV and vaccine immunogenicity, but rather more likely to reflect an altered immunosuppression regimen in those patients diagnosed with CAV. In our institution sirolimus is frequently prescribed alongside lower dose

tacrolimus and in place of mycophenolate mofetil in patients found to have CAV; this modified immunosuppression strategy may potentially underscore this association.

Ultimately, more studies are needed in larger populations to better phenotype these patients at most risk of reduced or absent humoral response. Moreover, the most recent joint statement (13th March 2022) from the ISHLT/AST/ASTS notes that although the use of antiproliferative agents have been implicated as a factor in poor antibody response after vaccination, there is no reliable guide for adjustment of immunosuppression in anticipation of vaccine responses.[17]

5 | LIMITATIONS

The analysis of humoral response in isolation is limited as the influence of cell mediated immunity on vaccination response cannot be appreciated. In addition, although in keeping with published similar studies, the threshold for a positive antibody response of 0.8 U/ml remains arbitrary, and the exact antibody threshold required to ensure protection against SARS-CoV-2 is unknown at this time. Furthermore, it is unclear if those with detectable antibodies after vaccination have neutralizing antibody titres effective against SARS-CoV-2. Finally, despite best efforts including the use of chart review, questionnaires, and the inclusion of antinucleocapsid antibody testing, patients with prior undetected asymptomatic SARS-CoV-2 may have been included as the prevalence of SAR-CoV-2 infection was high in the community for the duration of the study.

6 | CONCLUSIONS

Heterologous prime-booster vaccination against SARS-CoV-2 in heart transplant recipients is safe and significantly increased the number of patients with a detectable antibody response. However, over 40% continued to not show a detectable antibody response following their 3rd dose "booster" regimen. These findings highlight the importance of maintaining protective measures for transplant recipients- particularly those on more intensive immunosuppressive regimens - both at a personal and public health level, as well as investigating additional vaccine strategies, such as 4th dose recommendations already in place and/or development of more targeted vaccines for this cohort.

AUTHOR CONTRIBUTIONS

Developed concept for the study, consented patients, collected blood samples, performed literature review, and lead author on writing the final manuscript: Richard Tanner. *Collected blood samples, performed statistical analysis for the paper, and contributed to writing the manuscript*: Neasa Starr. *Collected blood samples and demographic patient data, provided editing, and full review of the paper before submission*: Carlos Nicolas Perez-Garcia. *Contributed to the literature review and advised on assay use, had role in writing the results and editing of the final manuscript before submission*: Grace Chan. *Analyzed all blood samples and provided guidance on interpretation of results, reviewed and edited manuscript before submission*: Emma Heffernan. *Co-ordinated the scheduling of blood sampling and contributed to blood sampling, reviewed and edited manuscript before finalization*: Eimear Dempsey. *Contributed to analysis and interpretation of results, provided edits for the main manuscript, and reviewed it before submission*: Breda Lynch. *Senior advisor for the study on assessment of antibody response after vaccination, contributed to planning of study protocol, and editing of final manuscript*: Margaret Hannan. *Senior author and provided guidance on all aspects of the study, developed concept for the study, contributed to planning of study protocol, consented patients, and drafting and editing of final manuscript*: Emer Joyce.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflict of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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