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#### ORIGINAL PAPER

# Impaired humoral and cellular response to primary COVID-19 vaccination in patients less than 2 years after allogeneic bone marrow transplant

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### Summary

Allogeneic haematopoietic stem cell transplant (HSCT) recipients remain at high risk of adverse outcomes from coronavirus disease 2019 (COVID-19) and emerging variants. The optimal prophylactic vaccine strategy for this cohort is not defined. T cell-mediated immunity is a critical component of graft-versus-tumour effect and in determining vaccine immunogenicity. Using validated anti-spike (S) immunoglobulin G (IgG) and S-specific interferon-gamma enzyme-linked immunospot (IFNy-ELIspot) assays we analysed response to a two-dose vaccination schedule (either BNT162b2 or ChAdOx1) in 33 HSCT recipients at ≤2 years from transplant, alongside vaccine-matched healthy controls (HCs). After two vaccines, infectionnaïve HSCT recipients had a significantly lower rate of seroconversion compared to infection-naïve HCs (25/32 HSCT vs. 39/39 HCs no responders) and had lower Sspecific T-cell responses. The HSCT recipients who received BNT162b2 had a higher rate of seroconversion compared to ChAdOx1 (89% vs. 74%) and significantly higher anti-S IgG titres (p = 0.022). S-specific T-cell responses were seen after one vaccine in HCs and HSCT recipients. However, two vaccines enhanced S-specific T-cell responses in HCs but not in the majority of HSCT recipients. These data demonstrate limited immunogenicity of two-dose vaccination strategies in HSCT recipients, bolstering evidence of the need for additional boosters and/or alternative prophylactic measures in this group.

#### K E Y W O R D S

allogeneic bone marrow transplant, BNT162b2, ChAdOx1, coronavirus disease 2019 (COVID-19), haematopoietic stem cell transplant (HSCT), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), T-cell response, vaccines

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# INTRODUCTION

The emergence of the Omicron variant of coronavirus disease 2019 (COVID-19) has once again highlighted the importance of understanding COVID-19 vaccine immunogenicity. As concerns mount that this and future variants may be partially resistant to antibody mediated protection, focus is shifting to better understanding the role of T cells in providing long-term protection from severe illness. This is especially relevant for patients with haematological cancer where prior therapies mitigate against a robust humoral response,<sup>1-4</sup> and in the context of documented waning of antibody responses to COVID-19 vaccines over time.<sup>5</sup> Furthermore, the relaxation of public health measures in several countries, including the UK, only acts to increase the necessity of immunogenic COVID-19 vaccines that protect vulnerable populations. COVID-19 vaccines have been shown to be highly protective against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and induce high levels of anti-SARS-CoV-2 Spike protein (S) antibodies.<sup>6-8</sup> However, immunocompromised groups including patients with haematological cancer have been widely shown to have reduced vaccine immunogenicity<sup>9</sup> and efficacy<sup>10</sup> and continue to be at inherent risk from COVID-19 infection.<sup>4</sup> Allogeneic bone marrow transplant (BMT; haematopoietic stem cell transplant [HSCT]) recipients within 2 years of transplant, and those who have had or are receiving additional T-cell suppressive therapies may be particularly at risk.<sup>11,12</sup>

The immunogenicity of the different COVID-19 vaccines in haematological patients has been studied, with a reduced response noted in comparison to patients with solid cancer and non-cancer controls.<sup>1</sup> Decreased immunogenicity was particularly evident in people with B-cell malignancies, due to the disease itself and the use of Bruton tyrosine kinase inhibitors, anti-CD20 monoclonal antibodies, and CD19targeted chimeric antigen receptor T-cell therapy.<sup>13</sup> In the HSCT setting, therapies with an even more profound longterm immunosuppressive effect are commonly utilised and these patients are known to have a particularly poor outcome following COVID-19 infection.<sup>11,12</sup> The response to COVID-19 vaccines in HSCT recipients has to date focused mainly on serological responses in recipients who received messenger RNA (mRNA) vaccination.<sup>14-18</sup> What remains unknown is how the SARS-CoV-2-specific T-cell response, important in modulating disease severity and determining vaccine immunogenicity, responds in HSCT recipients at  $\leq$ 2 years after transplantation and how this correlates with SARS-CoV-2-specific serological responses.

Our study evaluates the SARS-CoV-2-specific T-cell and antibody responses to AZD1222 (ChAdOx1 nCoV-19) and BNT162b2 in HSCT recipients at <2 years after transplantation. Using a control group of ChAdOx1 and BNT162b2 vaccinated healthy controls (HCs), we compare the immunogenicity of COVID-19 vaccines in HSCT compared with HCs and identify differences in vaccine responses following one (V1) and two doses (V2) of ChAdOx1 and BNT162b2 vaccine. We additionally identify clinical characteristics of HSCT recipients associated with anti-S antibody response after two doses of vaccine. As HSCT recipients receive multiple immunosuppressive regimens that differ in terms of immune targets/duration of effect, our study presents data on both SARS-CoV-2-specific antibody and T-cell responses to address the complex interplay between immune reconstitution, graft-versus-host disease (GVHD) prevention and response to vaccination.

# METHODS

## Study design and patients

This prospective observational cohort study received full approval from the University of Oxford Human Resources and Ethics committee (Ref Number: 17/SC/0572) and was conducted in accordance with International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice and the Human Tissue Act 2004. Participants were identified from the Oxford University Hospitals NHS Trust Bone Marrow Transplantation Unit Outpatient Department between the 1 December 2020 and 31 July 2021. Patients within 2-years of BMT (calculated from the date of stem cell infusion), able to give consent and eligible for standard-of-care SARS-CoV-2 vaccination were considered eligible. Participants were vaccinated at least 2 months after HSCT and were deemed clinically suitable for vaccination by their physician. Participants were enrolled in the study following signing of the informed consent form. A total of 38 patients were enrolled in this study of whom 33 were included in the vaccine immunogenicity analysis (Figure S1). SARS-CoV-2 antibody analysis was carried out at baseline and again 4-8 weeks after each vaccine dose (Figure S2). This broad time-window allowed patient samples to be collected during routine outpatient clinic follow-up and avoid unnecessary hospital attendances during the national lockdown. Vaccine immunogenicity results in the HSCT cohort were compared to that of vaccine-matched HCs, the data for which was obtained from the Protective Immunity from T cells to COVID-19 in Health workers (PITCH) study (Trial ID:252 ISRCTN11041050).

## Vaccine safety analysis

Vaccine safety analysis was performed by direct interview with all participants at the time of respective postvaccination sample collection after V1 and V2. Adverse events were graded according to Common Terminology Criteria for Adverse Events 5.0 and European Society for Blood and Marrow Transplantation (EBMT)-National Institutes of Health (NIH)-Center for International Blood and Marrow Transplant Research (CIBMTR) Task Force position statement on standardised terminology and guidance for GVHD assessment. Relationship of toxicity to vaccination was defined according to World Health Organization criteria (certain, probable, possible, and unlikely; http://who-umc.org/Graphics/24734.pdf).

# SARS-CoV-2-specific antibody and T-cell analysis

For the purpose of this study, serum antibody analysis was performed using the hospital standard-of-care assay. Both serum and peripheral blood mononuclear cells (PBMCs) were collected at the prespecified time points after vaccination and cryopreserved in the Oxford Haematology Biobank before analysis.

Antibodies against the SARS-CoV-2 S and nucleocapsid (N) proteins were measured using the Abbott AdviseDx SARS-CoV-2 immunoglobulin G (IgG) II. Briefly, this chemiluminescent microparticle immunoassay provides qualitative and semi-quantitative detection of IgG antibodies to SARS-CoV-2 in human serum and plasma, samples with responses >25000 arbitrary units (au)/ml were diluted. A SARS-CoV-2 anti-S IgG titre threshold of <50 au/ml was classified as 'no response' as per manufacturer guidelines, and <1000 au/ml was defined as 'low-response' using a cutoff previously defined as the equivalent to the lower limit of anti-S Ig generated after two vaccines in >90% of the PITCH (HCs) cohort.

Interferon-gamma (IFNy) enzyme-linked immunospot (ELISpot) assays were prepared from cryopreserved PBMCs using the Human IFNy ELISpot Basic kit (Mabtech 3420-2A). This methodology was adopted from the previously published PITCH study standard operating procedure.<sup>19</sup> MultiScreen-IP filter plates (Millipore, MAIPS4510) were coated with 50 µl/well using the ELISpot basic kit capture antibody (clone 1-D1K) at 10 µg/ml diluted in sterile Dulbecco's phosphate-buffered saline (DPBS; Fisher Scientific) for 3 h at room temperature. PBMCs were thawed and rested for 3h in RPMI media (Sigma) supplemented with 10% (v/v) heatinactivated human serum (Sigma), 1% (v/v) L-glutamine (Sigma), 1% (v/v) penicillin/streptomycin (Sigma) and DNase (Roche) at 37 C, prior to stimulation with peptides. The capture antibody coated plates were washed four times with sterile DPBS, then blocked with RPMI media supplemented with 10% (v/v) heat-inactivated human serum and 1% (v/v) penicillin/streptomycin for 2h at 37°C. Overlapping peptide pools (18-mers with 10 amino acid overlap. Mimotopes) representing spike S1 and S2, membrane (M) or N SARS-CoV-2 proteins were added to 200000 PBMCs/well at a final concentration of 2 mg/ml for 16-18 h. Pools consisting of cytomegalovirus, Epstein-Barr virus and influenza peptides at a final concentration of 2 mg/ml (CEF; Proimmune) and concanavalin A (Con A; Sigma) were used as positive controls. Dimethyl sulphoxide (DMSO) was used as the negative control at the equivalent concentration to the peptides. Wells were then washed six times with PBS with 0.05% (v/v) Tween20 (Sigma Aldrich) and incubated with the ELISpot basic kit biotinylated detection antibody (clone 7-B6-1) diluted in DPBS to a final concentration of 1 µg/ml, for 2h at

room temperature. Wells were then washed six times with PBS with 0.05% (v/v) Tween20, and then incubated with the ELISpot Basic kit streptavidin-ALP, diluted in PBS at 1 µg/ml for 1.5 h at room temperature. Wells were then washed with PBS and colour development was carried out using the one-step NBT/BCIP (nitro-blue tetrazolium/5-bromo-4-chloro-3-indolyphosphate) substrate solution; 50 µl of filtered NBT/ BCIP was added to each well for 10 min at room temperature. Colour development was stopped by washing the wells with tap water. Air-dried plates were scanned and analysed with the AID Classic ELISpot reader (software version 8.0, Autoimmune Diagnostika GmbH, Germany). Antigen-specific responses were quantified by subtracting the mean spots of the control wells from the test wells and the results are expressed as spot-forming units (SFU)/10<sup>6</sup> PBMCs.

### STATISTICAL ANALYSIS

Statistical analyses were done using R version 4.0.2 and GraphPad Prism 9.3.1. Continuous variables are summarised with median and interquartile range (IQR). Paired comparisons were performed using the Wilcoxon matchedpairs signed-rank test. Unpaired comparisons across two groups were performed using the Mann-Whitney U-test. Numbers and frequencies were computed for categorical variables, and comparisons between frequencies were made using Fisher's exact test. Two-tailed significance values are displayed and p < 0.05 was considered statistically significant. Uni- and multivariable linear regression models were used to investigate factors associated with serum post-V2 anti-S. Models were not performed on post-V2 S1+S2 IFNy T-cell response as the number of samples with this experimental readout was insufficient to produce statistically robust models. Factors were included in multivariable models based on strength of univariable associations (specifically where p < 0.1) and/or a priori biological evidence and clinical significance. Factors were only included in multivariable models if observations were recorded completely across all participants. For relevant factors where observations were not complete across participants, univariable associations with post-V2 anti-S IgG are presented.

### RESULTS

### **Study cohort**

A total of 38 patients who had undergone transplant at  $\leq 2$  years prior to date of enrolment were included (Figure S1). All patients underwent baseline SARS-CoV-2-specific antibody testing with follow-up antibody and T-cell reactivity testing planned for 4–8 weeks after each vaccination (Figure S2). Given the national UK lockdown during planned recruitment, this time-window allowed co-ordination of follow-up study visits with the individual patient's routine outpatient appointments. Five patients did not undergo post-V2



SARS-CoV-2 anti-S IgG measurement and were excluded from the immunogenicity analysis. Of the patient samples analysed, five samples were insufficient for SARS-CoV-2specific T-cell IFN $\gamma$ -ELISpot analysis. Therefore, the final analysis included 33 patients with post-V2 antibody titres, and 28 patients with both antibody and IFN $\gamma$ -ELISpot titres (Figure S1). All 38 subjects enrolled were included in the vaccine safety analysis. Each transplant subject was matched 1:1 to vaccine-type HCs, identified from the PITCH study.<sup>19</sup>

### **Baseline characteristics**

Baseline characteristics of the 33 patients included the vaccine immunogenicity analysis are presented in Table 1. The median (range) age of the patient population was 57 (19-70) years and 36% (12/33) were female. The majority (94%, 31/33) of patients, were of White British ethnicity. Regarding baseline immune function, 42% (14/33) of patients were lymphopenic (absolute lymphocyte count  $<1 \times 10^{9}$ /l) and 30% (10/33) had immunoparesis (baseline IgG <5 g/l). Allogeneic BMT indications included: 55% (18/33) for acute myeloid leukaemia (AML); 15% (five of 33) for myelodysplastic syndrome (MDS); 9% (three of 33) for myeloproliferative neoplasms (MPN); 9% (three of 33) for non-Hodgkin lymphoma; 6% (two of 33) for an MDS/ MPN overlap syndrome; 3% (one of 33) for Hodgkin lymphoma; and 3% (one of 33) for multiple myeloma. In all, 91% of patients (30/33) had a HSCT comorbidity index score of  $\leq 2$ . Stem-cell source was matched-unrelated donors (MUD) in 76% (25/33) of patients and matched-related donors (MRD) in 21% (seven of 33). Reduced-intensity conditioning was utilised pretransplant in 94% (31/33) of patients with only two patients (6%) receiving myeloablative therapy. With respect to specific T-cell depletion, 61% (21/33) of patients received alemtuzumab, 12% (four of 33) anti-thymocyte globulin and 3% (one of 33) received both. Primary vaccination was with AZD1222 and BNT162b2 in 73% (24/33) and 27% (nine of 33) of patients respectively. At V1 53.5% (15/33) of patients were <12-months post-HSCT. In all, 30% (10/33) of patients were being managed for active Grade  $\geq 2$  GVHD; seven patients with cutaneous disease, one with gastrointestinal, one with liver and one patient with combined cutaneous and liver. In all, 39% (13/33) of patients were taking continuous immunosuppression during the vaccination period, including 15% (five of 33) on oral corticosteroids.

# Serological response to COVID-19 vaccination in HSCT recipients

Anti-S IgG titres were measured using an Abbott SARS-CoV-2 IgG II quantitative antibody assay in recipients of allogenic HSCT and in HCs following one and two doses of ChAdOX1 or BNT162b2 (Figure 1). One HSCT recipient who was seropositive for anti-SARS-CoV-2 N protein upon vaccination was excluded from the immunogenicity analysis. The median 
 TABLE 1
 Demographic data of allogeneic haematopoietic stem cell transplant cohort included in immunogenicity analysis

Variable	Value
Number of HSCT recipients	33
Age, years, median (range)	57 (19–70)
Gender, <i>n</i> (%)	
Male	21 (64)
Female	12 (36)
Ethnicity, n (%)	
White British	31 (94)
Asian	-
African	-
Other	2 (6)
Baseline immune function, <i>n</i> (%)	
Lymphopenia	14 (42)
Immunoparesis (Total Ig)	10 (30)
HSCT Indication, <i>n</i> (%)	
AML	18 (55)
NHL	3 (9)
HL	1 (3)
ММ	1 (3)
MDS	5 (15)
MPN	3 (9)
MDS/MPN overlap	2 (6)
HSCT comorbidity index score, <i>n</i> (%)	
0	26 (79)
1	3 (9)
2	1 (3)
3	2 (6)
4	1 (3)
HSCT donor type, <i>n</i> (%)	
MUD	25 (76)
MRD	7 (21)
Haploidentical	1 (3)
HSCT conditioning, <i>n</i> (%)	
RIC	31 (94)
Myeloablative	2 (6)
TBI	
No	31 (94)
Yes	2 (6)
T-cell depletion, <i>n</i> (%)	
Alemtuzumab	20 (61)
ATG	4 (12)
ATG + Alemtuzumab	1 (3)
None	8 (24)
Vaccination, n (%)	
AZD1222	24 (73)
BNT162b2	9 (27)

#### TABLE 1 (Continued)

Variable	Value
Time since HSCT at V1, $n$ (%)	
<12 months	16 (48)
12–24 months	17 (52)
GVHD Grade $\geq 2, n$ (%)	
None	23 (70)
Acute	0 (0)
Chronic	10 (30)
Gut	1
Cutaneous	7
Liver	1
Gut + Skin	1
DLI at time of V1, <i>n</i> (%)	
Yes	4 (12)
No	29 (88)
Continuous immunosuppression, $n$ (%)	
Yes	13 (39)
No	20 (61)
Immunosuppression, n (%)	
Corticosteroids	8 (24)
Topical corticosteroids	3
Oral corticosteroids	5
Ciclosporin	7 (21)
Tacrolimus	1 (3)
Ruxolitinib	1 (3)
Mycophenolate	0 (0)
Combination	5 (15)

*Note*: Lymphopenia defined as <1.0×10<sup>9</sup>/l; Immunoparesis defined as IgG <6 g/l. Abbreviations: AML, acute myeloid leukaemia; ATG, anti-thymocyte globulin; DLI, donor lymphocyte infusion; GVHD, graft-versus-host disease; HSCT, allogeneic haematopoietic stem cell transplant; HL, Hodgkin lymphoma; Ig, immunoglobulin; MDS, myelodysplastic syndrome; MM, multiple myeloma; MRD, matched-related donor; MPN, myeloproliferative neoplasm; MUD, matched unrelated donor; NHL, non-Hodgkin lymphoma; RIC, reduced-intensity conditioning; V1, first vaccine dose.

anti-S IgG titre was increased significantly by two doses of either ChAdOx1 or BNT162b2 vaccine compared to one dose in both HSCT recipients and HCs (HSCT ChAdOx1 *p* < 0.0001, HSCT BNT162b2 *p* = 0.0156; HCs ChAdOx1 *p* = 0.0003, HCs BNT162b2 p < 0.0001). In both HSCT recipients and HCs, the titre of anti-S IgG after two doses of BNT162b2 vaccine was significantly higher than two doses of ChAdOx1 vaccine (HSCT p = 0.0216, HCs p < 0.0001; Mann–Whitney U). The median (IQR) anti-S IgG titre of HSCT recipients following two doses of BNT162b2 vaccine was 9731 (970.8-29108) au/ml and following two doses of ChAdOx1 vaccine the median (IQR) anti-S IgG titre was 1061 (29-3696) au/ ml. In HCs, the median (IQR) anti-S IgG titre following two doses of BNT162b2 was 14995 (12563-25411) au/ml and following two doses of ChAdOX1 was 1663 (918-2492) au/ml. The median titre of anti-S IgG in recipients of HSCT was



not significantly different compared to HCs after two doses of either vaccine (BNT162b2 p = 0.140, ChAdOx1 p = 0.458). However, in HSCT recipients the proportion of no response and low response following two doses of ChAdOx1 (no response <50 au/ml, six of 23 [26%] and low response <1000 au/ ml, five of 23 [22%]) was higher than that seen following two doses of BNT162b2 vaccine (no response one of nine [11%], low response one of nine [11%]). Across both vaccines, there was a significantly different proportion of no or low response in the HSCT group compared with the HC group (HSCT no/ low response 13/32 [40.6%] vs. HC no/low response five of 39 [11.4%], p = 0.0054, Fisher's exact test) (Figure S3A). All of the HCs with low response received two doses of ChAdOx1 vaccine and none had an anti-S IgG titre of <1000 au/ml. To assess whether any variables were predictive of low or no response, we performed a categorical univariate analysis of age, gender, lymphopenia, lymphoparesis, vaccine type, <12 month since vaccination, GVHD and immunosuppression, stratified by low/no post-V2 Anti-S IgG response. In this analysis, there was no significant difference in the assessed characteristics in the low/no serological response group compared to the high serological response group (Table S1).

The median titre of anti-S IgG after one dose of either ChAdOx1 or BNT162b2 vaccine was significantly lower in HSCT recipients than in HCs (ChAdOx1 p = 0.0004, BNT162b2 p < 0.0001). Following one dose of either BNT162b2 or ChAdOx1, only 4% of HSCT recipients had an anti-S IgG titre >1000 au/ml compared with 89% of HCs BNT162b2 vaccinees and 27% of ChAdOx1 HC vaccinees.

# Diminished T-cell response in HSCT recipients compared to HCs

As well as anti-S IgG titres, we investigated T-cell responses to PBMCs using overlapping 18mer peptides covering the entire SARS-CoV-2 S1 and S2 domains and covering the entire SARS-CoV-2 N and M proteins in a validated<sup>19</sup> IFNy ELISpot. To give an overview of the total IFNy T-cell response to SARS-CoV-2 S, results shown here are cumulative S1 + S2. Responses to separate S1 and S2 pools in HSCT recipients were not significantly different; however, in HCs response to the S1 region of the S protein was significantly higher than the S2 region (Figure S4). As expected, the only responder to SARS-CoV-2 N+M peptide pools was the N seropositive patient removed from S1 + S2 serology analysis (data not shown). All study participants (HSCT and HCs) had a positive (non-zero) IFNy T-cell response to S1+S2 after two doses, indicating presence of at least a minimal T-cell response to SARS-CoV-2 S peptide (Figure 2). At the post-V2 time point, the magnitude IFNy T-cell response to S1+S2 after vaccination with BNT162b2 or ChAdOx1 vaccines was significantly lower in HSCT recipients (median = 43 SFU/10<sup>6</sup> PBMCs) compared to HCs vaccinated with the same vaccine (median = 253 SFU/ $10^6$  PBMCs, p = 0.0050). In HSCT recipients vaccinated with two doses of BNT162b2, IFNy T-cell responses to S1+S2 were lower





**FIGURE 1** Anti-spike antibody response to coronavirus disease 2019 (COVID-19) vaccines in HSCT recipients and HCs. Abbott anti-spike immunoglobulin G titre (arbitrary units [au]/ml) at 28–56 days after the first dose of vaccine (V1) and 28–56 days after the second dose of vaccine (V2) in HSCT recipients (grey dots) and HCs (red dots). Individuals were vaccinated with either two doses of ChAdOx1 nCoV-19 vaccine (left panel) or two doses of BNT162b2 vaccine (right panel). Bars and lines represent median and interquartile range. Statistical tests are Mann–Whitney *U*-test for unpaired comparisons and Wilcox signed-rank test between paired comparisons. HC, healthy control; HSCT, allogeneic haematopoietic stem cell transplant. p > 0.05, \*p < 0.05, \*\*p < 0.001, \*\*\*\*p < 0.0001.



**FIGURE 2** Cumulative anti-SARS-CoV-2 S1 and S2 specific IFN $\gamma$  T-cell responses to coronavirus disease 2019 (COVID-19) vaccines in HSCT recipients and HCs. Combined IFN $\gamma$  T-cell responses to peptide pools covering SARS-CoV-2 S1 and S2 by IFN $\gamma$  enzyme-linked immunospot assay in PBMCs of HSCT recipients (grey dots) and HCs (red dots) at 28–56 days after first vaccine (V1) and 28–56 days after second vaccine (V2). Individuals were vaccinated with either two doses of ChAdOx1 vaccine (left panel) or two doses of BNT162b2 vaccine (right panel). Data represent spot forming units (SFU)/10<sup>6</sup> PBMC. Bars and lines represent median and interquartile range. Statistical tests are Mann–Whitney *U*-test for unpaired comparisons and Wilcox signed-rank test between paired comparisons. HC, healthy control; HSCT, allogeneic haematopoietic stem cell transplant; IFN $\gamma$ , interferongamma; PBMCs, peripheral blood mononuclear cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2. ns = p > 0.05, \*\*p < 0.01.

Chronic GVHD

Lymphopenia

Immunoparesis

(N = 24)Post-V1 S1 + S2 IFNy

Immunosuppressive therapy

Post-V1 anti-S IgG titre

 $(SFU/10^{6}) (N = 24)$ Post-V2 S1 + S2 IFNy

 $(SFU/10^{6}) (N = 27)$ 

ABLE 2 Uni- and multivariable linear models of allogeneic haematopoietic stem cell transplant recipient post-second vaccination anti-severe acute spiratory syndrome coronavirus-2 spike immunoglobulin G titre							
	Univariable linear regression			Multivariable linear regression			
Variable	Estimate (±SEM)	t statistic	p	Estimate (±SEM)	t statistic	p	
Age	-144.4 (143.0)	-0.80	0.430	-17.1 (148.4)	-0.12	0.909	
Non-White ethnicity	-1570.5 (2419.0)	-0.65	0.521	-1304.0 (2722.4)	-0.48	0.637	
Male Gender	2265.8 (3630.4)	0.62	0.537	2224.8 (3691.6)	0.60	0.553	
Vaccine type (Pfizer)	11977.8 (3270.6)	3.66	0.001	10396.7 (4194.2)	2.48	0.022	
T-cell depletion	-3154.1 (4044.3)	-0.78	0.442	-708.1 (4811.2)	-0.15	0.884	
<12 months post-HSCT	-404.6 (3537.1)	-0.11	0.910	-1567.7 (4344.2)	-0.36	0.722	

0.883

0.580

0.279

0.068

0.092

0.945

0.132

0.15

-0.56

1.10

-1.90

1.76

0.07

1.56

565.6 (3814.9)

-2275.4 (4064.0)

3852.7 (3495.7)

-7049.2 (3717.9)

13.4 (7.6)

0.74 (10)

14.2 (9.1)

т r

Note: Post-V2 anti-spike immunoglobulin (Ig)G titre was used as the dependent variable, and HSCT recipient's age (continuous), ethnicity (categorical), sex (categorical),
vaccine type (categorical), T-cell depletion prior to HSCT (categorical), <12 months post-HSCT (categorical), chronic GVHD (categorical), presence of immunosuppressive
therapy at pre-V1 (listed in Table 1, not including topical corticosteroid; categorical), lymphopenia (<1.0×10 <sup>9</sup> /l; categorical) and immunoparesis (IgG <6 g/l; categorical) were
used as independent variables. For immunological parameters, post-V1 anti-S IgG and post-V1 and post-V2 S1 + S2-specific IFN 7T-cell responses were used as continuous
independent variables. Modelled values are displayed ± standard error of the mean (SEM), for continuous variables the estimate represents the change in post-V2 anti-S IgG
per unit of variable change. For categorical variables, the estimate represents the change in anti-S IgG associated with the named variable.

Abbreviations: GVHD, graft-versus-host disease; HSCT, allogeneic haematopoietic stem cell transplant; IFNy, interferon-gamma; SFU, spot-forming units; V1, first vaccine dose: V2, second vaccine dose.

compared to HCs vaccinated with two doses of BNT162b2 but the difference was not statistically significant (HSCT, median = 29 SFU/10<sup>6</sup> PBMCs; HCs, median =  $158 \text{ SFU}/10^6$ PBMCs, p = 0.0552). Unlike the observed differences in anti-S IgG results between HCs and HSCT recipients, there was no significant difference in IFNγ T-cell response to S1 + S2 in HSCT recipients or HCs vaccinated with two doses of ChAdOx1 compared to those vaccinated with two doses of BNT162b2 (p = 0.743). IFN $\gamma$  T-cell responses to S1 + S2 in HSCT recipients did not significantly increase after two doses of either vaccine compared to one (ChAdOx1 p = 0.135, BNT162b2 p = 0.438); however, the magnitude of IFNy T-cell responses to S1 + S2 was significantly increased after two doses of either vaccine compared to one in HCs (ChAdOx1 p = 0.0078, BNT162b2 p = 0.0039). Using a cutoff defined by 2×the standard deviation of the assay negative (DMSO) across all IFNy ELISpots runs (cut-off = 20.7 SFU/10<sup>6</sup> PBMCs), we determined the number of no T-cell responders to S1 + S2 following two doses of vaccine. There was a significantly greater number of no T-cell responders to S1+S2 following two doses of either ChAdOx1 or BNT162b2 in the HSCT group than the HC group (29.6% HSCT vs. 3.3% HC, *p* = 0.0095) (Figure S3B). A similar proportion of no T-cell responders to S1 + S2 were observed in HSCT recipients who received BNT162b2 vaccine (two of six [33.3%]) compared to ChAdOx1 vaccine (28.6%).

### Uni- and multivariable regression models of demographic characteristics with serological immunogenicity in HSCT recipients

0.50

-0.69

0.18

-1.74

2198.9 (4420.7)

-3431.1 (4962.8)

756.5 (4258.7)

-6719.6 (3867.3)

We analysed the association of clinical and demographic characteristics in the HSCT cohort to investigate factors associated with post-V2 anti-S IgG titre (Table 2). Demographic factors analysed include age, gender, and ethnicity. Clinical factors included vaccine type, time since transplant (<12 vs. >12 months), treatment with immunosuppressive therapy at time of first vaccine, lymphopenia ( $<1.0 \times 10^9$  lymphocytes/l), immunoparesis (defined as total IgG <6 g/l), T-cell depletion (binary) and acute GVHD (binary). Due to the decreased number of participants with matched pre-V1 anti-S IgG and IFNy T-cell responses, linear regression using these immunological parameters was reserved only for univariate analysis and not included in the multivariable model. In uni- and multivariable linear regression models only vaccine type was significantly associated with anti-S IgG titre measured after two doses of COVID-19 vaccine. Post-V2 anti-S IgG titres in those with immunoparesis differed to those without; however, this difference was not significant in either uni- or multivariable analysis (p = 0.068, p = 0.097 respectively). Although found to be associated with increased mortality from COVID-19 infection,<sup>12</sup> time from transplant to vaccine (<12 months from transplant to V1) was not significantly associated with anti-S IgG titre after two doses of vaccine.

0.624

0.497

0.861

0.097



Notably, in univariable analysis the IFN $\gamma$  T-cell response to S1+S2 was not significantly associated with post-V2 anti-S IgG, although a one unit change in post-V2 S1+S2specific IFN $\gamma$  T-cell response was associated with a larger mean unit increase in serum post-V2 anti-S IgG compared to the post-V1 IFN $\gamma$  S1+S2-specific T-cell response. This suggests that the functional T-cell response following first vaccine dose in HSCT recipients was not predictive of antibody response following second vaccination. Anti-S IgG following the first vaccine dose in HSCT recipients was also not significantly associated with post-V2 anti-S IgG (p = 0.092), likely due to the large number of HSCT recipients whose response was not significantly boosted following a second dose of COVID-19 vaccine.

## Vaccine safety

Of the 38 patients included in the safety analysis only one patient experienced a Grade 3 adverse event: injection site tenderness with significant discomfort at rest requiring review and analgesia (Table 3). Grade  $\leq 2$  localised reactions were common, with 39% (15/38) of patients reporting injection site pain and 24% (nine of 38) reporting tenderness. Systemic reactions were reported by 26% (10/38) of patients, commonly Grade 1; 13% (five of 38) fever and 8% (three of 38) rigours. Two patients experienced Grade 2 flares of their preexisting GVHD requiring medical review/management: one respiratory and one cutaneous. However, both reactions occurred following a recent reduction in immunosuppression and it was therefore judged that vaccination alone was unlikely to be the sole explanation for symptoms. Furthermore, both patient's symptoms improved with re-introduction of GVHD therapy.

# DISCUSSION

The EPICOVIDEHA prospective registrational study (ClinicalTrials.gov Identifier: NCT04733729) highlighted the increased risk of re-infection in vaccinated patients with haematological cancer, demonstrating a 21.3% intensive care admission rate and 12% 30-day mortality.<sup>4</sup> This, and other studies that highlight the increased risk of mortality from SARS-CoV-2 in HSCT recipients,<sup>11,12</sup> demonstrate the need for an effective vaccine that protects vulnerable groups from symptomatic infection and death. The Oxford/ AstraZeneca (ChAdOx1 nCoV-19) vaccine and Pfizer/ BioNTech (BNT162b2) vaccine have been shown to be effective and immunogenic in several large studies since their

 TABLE 3
 Adverse events after vaccination in allogeneic haematopoietic stem cell transplant cohort

	Total patients $n = 38$					
	Localised <sup>a</sup> Patients reporting AEs (n = 22 [58%])					
Symptom	Grade 1	Grade 2	Grade 3	Grade 4		
Pain	14	1				
Tenderness	7	2	1			
Erythema						
Induration						
	Systemic <sup>b</sup> Patients reporting AEs ( <i>n</i> = 10 [26%])					
	Grade 1	Grade 2	Grade 3	Grade 4		
Fever	5					
Tachycardia						
Myalgia	3					
Breathlessness						
Rigours	1					
Headache	1					
Flare of GVHD		2 <sup>c</sup>				
Respiratory		1				
Cutaneous		1				

*Note:* All adverse events (AEs) were recorded following direct interview with patients at the time of blood sampling and graded as per common terminology criteria for AE (CTCAE v4.3).

Abbreviations: GVHD, graft-versus-host disease.

<sup>a</sup>Three patients experienced a combination of pain and tenderness.

<sup>b</sup>Four patients experienced a combination fever and myalgia.

<sup>c</sup>Both patients had recently had a reduction in immunosuppression therefore the association with vaccination was judged unlikely.

development<sup>20-22</sup> including against variants of concern.<sup>23</sup> However, many of the studies that look to demonstrate the effectiveness of COVID-19 vaccines have done so in a cohort of healthy individuals who are not immunocompromised. As such, the vaccine immunogenicity demonstrated in these studies may not be representative of responses in individuals with reduced immunological capacity.

Reduced immunogenicity of vaccines in immunocompromised individuals has been reported in several highly vulnerable groups to date,<sup>9,24-26</sup> including HSCT recipients.<sup>18,27</sup> Most of the existing studies that have investigated the immunogenicity of vaccines in HSCT recipients focus on anti-SARS-CoV-2 S antibodies; however, few directly compare vaccine platforms (ChAdOx1 vs. BNT162b2) at unified time points. Here, we use a validated and commercially available SARS-CoV-2 S IgG assay (Abbott IgG II) to measure antibody responses to two doses of ChAdOX1 or BNT162b2 in HSCT recipients and vaccine-matched HCs. Our analysis demonstrates a significantly reduced seroconversion rate in HSCT recipients after two doses of ChAdOx1 vaccine compared with the same vaccine in HCs, as established in previous studies.<sup>1,5,19</sup> In addition, despite the limited sample size, vaccination with BNT162b2 was associated with a significantly higher overall anti-S IgG titre in both HSCT recipients and HCs. This is consistent with other studies, which show that mRNA vaccines such as BNT162b2 induce higher magnitude anti-S antibody after two doses of vaccine in healthy people.<sup>28</sup>

We used uni- and multivariable linear regression models to investigate clinical and demographic factors associated with anti-S IgG titre after two doses of COVID-19 vaccine in HSCT recipients. Only vaccine type was significantly associated with anti-S IgG titres in the multivariable model (Table 2). Although not significant, immunoparesis at the pre-V1 time point was associated with a reduced post-V2 anti-S IgG titre (p = 0.097); however, neither immunosuppressive therapy at the time of vaccination or <12 months post-HSCT were significantly associated with reduced anti-S IgG after second vaccine (p = 0.497, p = 0.722 respectively), although this finding may be as a result of the small sample size in this study. It may be that the B-cell compartment and subsequent COVID-19 vaccine response in these HSCT recipients was not substantially altered by time since transplant or presence of immunosuppressive therapy. A larger cohort of HSCT recipients and further investigation of overall Bcell responses in these patients would be required to validate this finding. Indeed, other large studies investigating antibody responses to COVID-19 vaccines in HSCT recipients found that immunosuppressive therapy significantly decreased serological response to vaccine in HSCT recipients.<sup>15,18,29</sup> Furthermore, no patients in our cohort received mycophenolate mofetil or Janus kinase inhibitors, both of which have been shown to significantly reduce serological response to COVID-19 vaccine.<sup>30,31</sup>

In the context of the new variant of concern, the Omicron variant, which has been shown to evade neutralisation by antibodies mounted to both ChAdOx1 vaccine and BNT162b2,<sup>23</sup> it is likely that measurement of the immune response by investigating anti-S antibodies alone is insufficient to demonstrate effective vaccine immunogenicity. While it is apparent that the vaccine-induced antibody response to the Omicron variant of SARS-CoV-2 is diminished, emerging evidence has demonstrated the conservation of T-cell responses to Omicron S.<sup>23,32,33</sup> Considering the reduced burden of infection with Omicron variant compared with subsequent variants of SARS-CoV-2<sup>34</sup> it is likely that T cells play an important role in protecting against severe disease and therefore represent an important marker of the immune response to SARS-CoV-2.

Studies investigating the IFNy T-cell response to SARS-CoV-2 vaccination have shown robust and sustained responses to mRNA vaccine in healthy people<sup>19</sup>; however, to date and to the best of our knowledge, there have been no studies measuring and comparing the cellular response (SARS-CoV-2 S-specific IFNy T-cell response) to COVID-19 vaccination with both ChAdOx1 and BNT162b2 vaccines in HSCT recipients. Here, functional SARS-CoV-2 S-specific T-cell responses were measured by ex vivo stimulation of PBMCs from HSCT recipients and HCs by overlapping peptide pools covering the entirety of SARS-CoV-2 S1 and S2 domains in an IFNy ELISpot assay. The magnitude of SARS-CoV-2 S-specific IFNy-releasing T cells were reduced overall in HSCT recipients that received either ChAdOx1 or BNT162b2 vaccine, although the small sample size of the HSCT BNT162b2 vaccinees in this study limits the statistical power of this finding. Despite having reduced responses, all HSCT recipients had detectable functional IFNy T-cell responses after two doses of vaccine suggesting they had at least a minimal SARS-CoV-2 S-specific response to vaccination. It is currently unclear what level of T-cell response is required to reduce disease severity and correlates of protection against SARS-CoV-2 infection remain unknown; however, it is possible that the lower number of functional T cells after vaccination leaves HSCT recipients at a higher risk of severe disease. Directly linking the SARS-CoV-2-specific IFNy T-cell response from vaccination to subsequent protection against symptomatic SARS-CoV-2 infection is challenging, especially in the context of HSCT.

Interestingly, there was no appreciable increase in the magnitude of SARS-CoV-2 S-specific IFNγ-releasing T cells after two doses of COVID-19 vaccine compared to one dose of vaccine in HSCT recipients. Unlike the HCs, who had significantly increased SARS-CoV-2 S-specific T-cell responses after two doses of vaccine compared to one. In the context of the Omicron variant, where the conservation of SARS-CoV-2-specific T cells are thought to be connected with reduction in disease severity this highlights a potential risk for HSCT recipients.<sup>23</sup> Further study must be done to investigate the SARS-CoV-2-specific T-cell response after third doses of vaccine to assess the capacity of further vaccines to boost T-cell responses.

There are several limitations to this study, including the limited sample size of the BNT162b2 cohort and the relative heterogeneity in time from vaccine to response assessment (28-56 days post-vaccine). It is possible that with an increased sample size, additional non-responders in the BNT162b2 HSCT group may have been reported, and that the linear regression models may have identified additional parameters linked to post-V2 anti-S IgG. Despite being able to match by vaccine type, we were unable to match the age of the HCs to the HSCT cohort (median [IQR] age of HSCT recipients 57[52-64] vs. 29 [22-42] years in HCs), although the age range of participants included in each group was similar (age range of HSCT recipients 19-71 vs. 21-63 years in HCs) and as seen in Table 2, age was not significantly associated with serological response after two doses of vaccination. Due to limitations in the sample size (n < 30), we were unable to investigate factors associated with post-V2 anti-S IgG by multivariable linear regression, which included immunological outputs (post-V1 anti-S IgG, or post-V1/V2 S1 + S2-specific IFNy T-cell response). Also, as we only used IFNy ELISpots and were limited by PBMC counts, we were unable to further determine which SARS-CoV-2-specific T-cell subset (CD4/CD8) was functionally active, and we were limited to detecting only IFNy-type responses and no other functional T-cell markers (interleukin [IL]-4/IL-2 etc.).

Studies that have investigated third doses of vaccines in HSCT recipients have highlighted the potential value in adding an additional vaccine dose to the vaccine regimen for HSCT recipients.<sup>27,29</sup> From these studies, it is clear that many patients who do not seroconvert after two vaccines will seroconvert after three. However, it remains likely that some patients who remain on immunosuppressants and who do not respond to two doses of vaccine (six of 23 ChAdOx1 HSCT vaccinees in this study) will continue to fail to seroconvert after subsequent vaccine doses.<sup>27,29</sup> As such, and as a response to the data presented here and that gathered from other UK-based studies in immunocompromised cohorts, NHS England has released guidance for clinically extremely vulnerable patients who test polymerase chain reaction positive for COVID-19. This cohort (including those post allogeneic BMT) will be fast-tracked for therapy with SARS-CoV-2 neutralising monoclonal antibodies,<sup>35</sup> such as sotrovimab<sup>36</sup> or Evusheld<sup>™</sup> (tixagevimab co-packaged with cilgavimab). In addition, hospitalised patients will continue to receive remdesivir as per previously published guidance.<sup>37</sup> However, the true long-term efficacy of these novel anti-viral therapies in immunocompromised cohorts remains to be studied.

Despite the limitations of this study, we show here that both antibody and T-cell responses to COVID-19 vaccines are reduced in patients after HSCT compared with HCs. Allogeneic BMT recipients remain exposed to severe COVID-19 infection, especially in the context of emerging variants, due to both reduced SARS-CoV-2-specific antibodies (in the case of ChAdOx1) and T-cell responses. Further studies with increased numbers of participants are required to fully understand the correlates of reduced immunogenicity in HSCT recipients. Furthermore, it is important that future studies immunophenotype disease cohorts in detail to understand the underlying context of vaccine nonresponsiveness in these patients. In the context of widespread use of third and fourth COVID-19 vaccine doses in HSCT recipients, it is important to understand the effect that these have on SARS-CoV-2-specific immune responses, especially with heterologous vaccinations. Where vaccines do not boost immunogenicity that is protective against infection, studies such as this should be used to guide therapeutic options for clinically vulnerable groups.

### AUTHOR CONTRIBUTIONS

Conceptualisation: Murali Kesavan, Eleanor Barnes; Methodology: Eleanor Barnes, Susanna Dunachie, Cori Campbell; Software: Cori Campbell, Sam M. Murray; Formal analysis: Sam M. Murray, Cori Campbell; Investigation: Sam M. Murray, Anthony Brown, Sandra Adele, Eloise Phillips, Tom Malone, Ali Amini, Maria Barbanti, Sally Springett, Lucia Chen, Jay Dhanapal, Bing Tseu, Omer Pervaiz, LP; Resources, Murali Kesavan, Lizzie Stafford, Maria Barbanti, Sally Springett, Lucia Chen, Jay Dhanapal, Bing Tseu, Omer Pervaiz, Louis Peters, Andrew Peniket, Robert Danby; Data Curation: Sam M. Murray, Murali Kesavan; Writing - Original draft: Sam M. Murray, Murali Kesavan, Maria Barbanti, Cori Campbell; Writing - Review and editing: Eleanor Barnes; Visualisation: Sam M. Murray, Murali Kesavan; Supervision: Eleanor Barnes, Susanna Dunachie, Paul Klenerman; Project administration: Alexandra S. Deeks.

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### **CONFLICT OF INTERESTS**

The authors declare no conflicts of interest. Oxford University has entered a joint COVID-19 vaccine development partnership with AstraZeneca.

# RESOURCE AVAILABILITY

### Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Murali Kesavan, murali.kesavan@oncology.ox.ac. uk

### Materials availability

This study did not generate any new unique reagents.

### Data and code availability

The published article includes all data generated and analysed during this study. Data will be made available freely from the corresponding authors upon request.

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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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