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i An update to this article is included at the end

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Letter

Repeated vaccination against SARS-CoV-2 elicits robust polyfunctional T cell response in allogeneic stem cell transplantation recipients

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SARS-CoV-2 has led to unprecedented global healthcare challenges, with poor outcomes observed in groups with immune deficiency, including allogeneic stem cell transplantation (allo-SCT) recipients (Bakouny et al., 2020). T cell and B cell responses following vaccination against SARS-CoV-2 are important in reducing the risk of severe COVID-19, but the T cell response has not been extensively investigated in this population. We designed a prospective study to evaluate response to vaccination in patients with hematologic malignancies. Herein we report analysis of T cell and humoral response to sequential dosing of vaccination against SARS-CoV-2 in allo-SCT recipients.

Anti-SARS-CoV-2 Spike protein (S) IgG ELISA and neutralizing antibody testing were performed as described previously. The induction of virus-specific T cell responses by vaccination was assessed by flow-cytometric enumeration of antigen-specific $CD8^+$ and $CD4^+$ T lymphocytes using an intracellular cytokine assay for IFNγ and TNFα.

A total of 23 patients were analyzed at one or more time point around the two-dose vaccination schedule (Table S1). Median age was 55 years (range 25–74), and 69.6% (16) were male. Median time from allo-SCT was 55 months (19–172), and BNT162b2 vaccine was given to 81% (21) of patients, while others received ChAdOx1-S.

Following a first dose of vaccine, an anti-S IgG response was assessed in 18 patients at a median of 4.2 weeks after vaccination. Anti-S IgG was detectable in only 38.9% (7), with 4 of these having weak positive results (Figure S1A). A mean anti-S IgG EC_{50} of 76 (range 0–526) was observed at this time point (Figure S1B). Neutralizing antibody analysis was performed in all 7 patients with detectable anti-S IgG at this time point, with a mean ID50 of 292 observed (32–968) (Figure S1C).

Antibody testing was performed in 16 patients following two doses of vaccine, at a median of 12 weeks after the second dose. A detectable anti-S IgG was observed in 81% (13) of patients ($p \leq 0.017$) (Figure S1A), with a mean anti-S IgG of 1043 (0–5594) ($p = 0.025$) (Figure S1B). Neutralizing antibody testing performed in 13 patients with detectable IgG showed a mean ID50 of 747 (107–4707) (Figure S1C). After two doses of vaccine, antibody testing was performed in 10 patients with chronic graft-versus-host disease (GvHD) receiving extracorporeal photopheresis (ECP) and 6 patients not receiving ECP, with a mean EC_{50} of 574 in ECP group, compared with 1826 non-ECP ($p = 0.17$). Similarly, mean neutralizing antibody ID50 was 312 in those requiring ECP compared with 719 in non-ECP. There was a significant correlation between anti-S IgG level and neutralizing ability from paired samples, with r value of 0.83 ($p < 0.0001$) (Figure S1D).

T cell analysis was performed in 17 patients after a single dose of vaccine and in 17 patients after two doses. A T cell response was observed in 35.3% (6) of patients after one dose and in 82.3% (14) of patients after two doses ($p = 0.013$) (Figure S1E). A $CD4^+$ T cell response was observed in 29.4% (5) of patients after one dose and 70.6% (12) of patients after two doses ($p = 0.0.38$), while a $CD8^+$ T cell response was only seen in 17.6% (3) after one dose but 52.3% (9) after two doses ($p = 0.07$). Mean $CD4^+/CD8^+$ TNFα expression after a single dose was 0.12%/0.04%, which increased to 0.42%/0.13% after second dose ($p = 0.17/0.3$). Similarly, mean $CD4^+/CD8^+$ IFNγ expression after a single dose was 0.06%/0.03%, which again increased to 0.07%/0.17% ($p = 0.8/0.1$).

A polyfunctional T cell response, with dual expression of more than one proinflammatory cytokine within the same cell, was observed in 29.4% (5) of patients after one dose and 70.6% (12) after two doses ($p = 0.038$) (Figures S1F and S1G). After a single dose, mean $CD4^+$ polyfunctional T cell response was 0.009%, with an increase to 0.026% after 2 doses ($p = 0.068$) (Figure S1H). Consistently, more than 90% of reactive T cells expressing pro-inflammatory cytokines showed co-expression of CD45RO, a surface protein marker for memory T cells. After a second dose, patients with chronic GvHD requiring ECP had a mean $CD4^+$ TNFα expression of 0.18% compared with 0.86% in those not requiring ECP ($p = 0.09$) (Figure S1I).

Patients with prior allo-SCT who contract COVID-19 infection have poor outcomes, with overall survival reported at 68% at 30 days post diagnosis (Sharma

et al., 2021). Therefore, the development of immunity is particularly important in this patient group. We have previously reported that a single dose of BNT162b2 is sufficient to generate both a humoral and a T cell response in most patients with chronic myeloid malignancies (Harrington et al., 2021). This is in contrast to the response observed in many cancer-patient groups, particularly those with lymphoid malignancies who have received anti-CD20 targeted therapy (Addeo et al., 2021, Greenberger et al., 2021, Thakkar et al., 2021). We demonstrate here how a second dose is required for a significant increase in seroconversion rates and detectable memory T cells in allo-SCT recipients. Through analysis of samples at consecutive time points, including sequential samples from the same patients, we were able to observe the longitudinal response to vaccination and show that a second dose is required for adequate immunogenicity in this population. Our findings are in keeping with that from two studies on isolated antibody responses in allo-SCT patients which reported an anti-S IgG response after a second injection in 83% and 78% of participants, respectively (Redjoul et al., 2021, Le Bourgeois et al., 2021).

Our data report the T cell response to SARS-CoV-2 vaccination in patients with previous allo-SCT. Despite a poor T cell response after a first vaccine injection, a second dose elicited anti-S reactive T cells in most patients. Moreover, a polyfunctional T cell response was also elicited by a second dose, which may have particular functional relevance with regards to anti-viral immunity, with these cells recognized as providing a more effective anti-viral response in the context of COVID-19 infection (Peng et al., 2020). A memory T cell response may play a particularly important role in providing immunity to COVID-19, as studies have shown significant decline in antibody levels in the general population at 3 months post natural infection (Seow et al., 2020).

We have also focused our analysis on patients considered to be particularly immune suppressed with regards to chronic GvHD and ongoing systemic immune suppression. While these patients did show a reduced T cell and antibody response when compared with patients off immune suppression, this was not significant, and most showed an adequate neutralizing antibody response after a second injection. Our study is, however, limited by small sample size, and further longitudinal data are required to evaluate whether the response generated is adequate to provide anti-viral protection.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.10.002.

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AUTHOR CONTRIBUTIONS

P.H. and H.d.L. designed the research, performed the research, analyzed the data, and wrote the manuscript. K.J.D., T.L., H.K., and M.M. performed the research and reviewed the manuscript. F.C., R.D., S.S., K.R., D.M., D.A., , DA, S.K., C.H., and V.M. assisted with patient recruitment and reviewed the manuscript. C.S., J.S., A.O.R., and A.E. assisted with patient recruitment and patient interviews and reviewed the manuscript. V.M. and H.d.L. share senior authorship.

DECLARATION OF INTERESTS

P.H. received research funding from Bristol Myers Squibb and speaker fees from Incyte. D.M. received speaker fees and advisory boards Novartis, Celgene, and Jazz pharmaceuticals. S.K. received Celgene and Novartis research grant and Alexion speaker honorarium. C.H. received speaker fees from Novartis, Jannsen, CTI, Celgene, and Medscape and has served on the advisory board for Incyte, CTI, Sierra Oncology, Novartis, Celgene, Roche, AOP Pharma, Geron, and Astra Zenica. H.d.L. has received grants and speakers fees from Bristol Myers Squibb and Incyte and speaker fees from Novartis.

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Update

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Correction

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In this letter, we report the T cell response to SARS-CoV-2 vaccination in patients with previous allogeneic stem cell transplantation. Victoria Potter did not feel she made significant contribution to this work and requested not to be a co-author after publication. Daniele Avenoso participated in patient recruitment and is now included as an author. All other authors approved the changes, which are reflected in the online version of the letter.

