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

Patrick Harrington,1,2 Katie J. Doores,3 Chandan Saha,1 Jamie Saunders,1 Fiona Child,1 Richard Dillon,1,4 Sukran Saglam,1 Kavita Raj,1 Donal McLoman,1 Daniele Avenoso,2 Shahram Kordasti,1,2 Amy O’Reilly,1 Andreas Espehana,1 Thomas Lechmere,3 Hataf Khan,3 Michael H. Malim,3 Claire Harrison,1,2 Varun Mehra,5 and Hugues de Lavallade1,2,*

1Department of Clinical Haematology, Guy’s & St. Thomas’ NHS Foundation Trust, London, UK
2School of Cancer and Pharmaceutical Science, King’s College London, London, UK
3Department of Infectious Diseases, School of Immunology & Microbial Sciences, King’s College London, London, UK
4Department of Medicine & Molecular Genetics, King’s College London, London, UK
5Department of Haematological Medicine, King’s College Hospital, London, UK
*Correspondence: h.delavallade@nhs.net

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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 EC50 of 76 (range 0–526) was observed at this time point (Figure S1B). Neutralizing antibody analysis was performed in 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 ≤ 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 EC50 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 = 0.038), 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).

SUPPLEMENTAL INFORMATION

Seroconversion rates following COVID-19 vaccination in patients with cancer. Cancer Cell 39, 1031–1033, November 8, 2021

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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., D.A., 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 Aเล็กซัน speaker honorarium. C.H. received speaker fees from Novartis, Janssen, CTI, Celgene, and Mediscapte and has served on the advisory board for Incyte, CTI, Sierra Oncology, Novartis, Celgene, Roche, AOP Pharma, Geron, and Astra Zeneca. H.d.L. has received grants and speaker fees from Bristol Myers Squibb and Incyte and speaker fees from Novartis.

REFERENCES

Addeo, A., Shah, P.K., Bordry, N., Hudson, R.D., Albracht, B., Di Marco, M., Kaklamani, V., Dietrich, P.Y., Taylor, B.S., Simand, P.F., et al. (2021). Immunogenicity of SARS-CoV-2 messenger RNA vaccines in patients with cancer. Cancer Cell 39, 1091–1098.

Bakouny, Z., Hawley, J.E., Choueiri, T.K., Peters, S., Rini, B.I., Warine, J.L., and Painter, C.A. (2020). COVID-19 and cancer: current challenges and perspectives. Cancer Cell 38, 629–646.

Greenberger, L.M., Saltzman, L.A., Senefeld, J.W., Johnson, P.W., DeGennaro, L.J., and Nichols, G.L. (2021). Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. Cancer Cell 39, 1031–1033.

Harrington, P., Doores, K.J., Radia, D., O’Reilly, A., Lam, H.P.J., Seow, J., Graham, C., Lechmere, T., McLornan, D., Dillon, R., et al. (2021). Single dose of BNT162b2 mRNA vaccine against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induces neutralizing antibody and polyfunctional T cell responses in patients with chronic myeloid leukaemia. Br. J. Haematol. 194, 999–1006.

Le Bourgeois, A., Coste-Burel, M., Guillaume, T., Peterlin, P., Garnier, A., Béné, M.C., and Chevallier, P. (2021). Safety and antibody response after 1 and 2 doses of BNT162b2 mRNA vaccine in recipients of allogeneic hematopoietic stem cell transplant. JAMA Netw. Open. 4, e2126344.

Peng, Y., Mentzer, A.J., Liu, G., Yao, X., Yin, Z., Dong, D., Dejirrattisai, W., Rostron, T., Supasa, P., Liu, C., et al. (2020). Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent COVID-19 patients. bioRxiv, 2020.06.03.134551.

Redjoul, R., Le Bouter, A., Beckerich, F., Fourati, S., and Maury, S. (2021). Antibody response after second BNT162b2 dose in allogeneic H SCT recipients. Lancet 398, 298–299.

Seow, J., Graham, C., Merrick, B., Acors, S., Pickering, S., Steel, K.J.A., Hemmings, O., O’Bryne, A., Koupou, N., Gala, R.P., et al. (2020). Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. Nat. Microbiol. 5, 1596–1607.

Sharma, A., Bhatt, N.S., St Martin, A., Abid, M.B., Bloomquist, J., Chemaly, R.F., Dandoy, C., Gauthier, J., Gowda, L., Perales, M.A., et al. (2021). Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. Lancet Haematol. 8, e185–e193.

Thakkar, A., Gonzalez-Lugo, J.D., Goradia, N., Gali, R., Shapiro, L.C., Pradhan, K., Rahman, S., Kim, S.Y., Ko, B., Sica, R.A., et al. (2021). Seroconversion rates following COVID-19 vaccination among patients with cancer. Cancer Cell 39, 1081–1090.
Correction

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*Correspondence: h.delavallade@nhs.net
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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.