Impaired immune responses in blood cancers improved by third COVID-19 vaccine dose

People with lymphoma have immune defects that compromise the immune response to vaccination. A prospective observational study of 457 people with lymphoma showed improvement in antibody and T cell responses after the third vaccine dose except in those who received anti-CD20 antibody therapy within a year prior to vaccination.

This is a summary of:
Lim, S. H. et al. Immune responses against SARS-CoV-2 variants after two and three doses of vaccine in B-cell malignancies: UK PROSECO study. *Nat. Cancer* https://doi.org/10.1038/s43018-022-00364-3 (2022).

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The problem

Despite the gradual lifting of COVID-19 restrictions worldwide, a cloud continues to hang over immunosuppressed people, who may not develop protective immune responses after vaccination. In particular, people with hematological malignancies are at greater risk of severe COVID-19 disease despite vaccination[1]. Multiple studies have identified risk factors associated with poor vaccine responses, but most are compromised by intrinsic limitations in study design. Assessment of paired humoral and cellular responses in a large and clinically homogeneous cohort is critical to allow accurate characterization of vaccine immune response in these people. The other major concern in this population is whether the antibodies induced by vaccination will be effective against the SARS-CoV-2 variants of concern.

The observation

We conducted a multicenter, prospective observational cohort study (UK PROSECO) to coincide with the national SARS-CoV-2 vaccination program in the United Kingdom[2]. In adults with a confirmed diagnosis of lymphoma, peripheral blood samples were collected (where feasible) before vaccination with either ChAdOx1 nCoV-19 (ChAdOx1) or BNT162b2, 4 weeks after the first dose, 2–4 weeks and 24 weeks after the second dose, and 4–8 weeks after the third dose. The study aimed to evaluate the robustness of vaccine response and to identify predictors of immune response in people with lymphoma. This was achieved by measurement of antibodies to SARS-CoV-2 spike antigen (anti-S), the ability of these antibodies to inhibit the interaction between the viral spike protein and its host receptor ACE2 (pseudoneutralization), and release of the cytokine IFNγ by T cells stimulated with spike peptide[3–5].

We observed that 52% of people with lymphoma undergoing active anti-cancer treatment had undetectable antibody levels despite two vaccine doses (Fig. 1a). Those diagnosed with indolent B cell non-Hodgkin lymphoma (B-NHL) had reduced antibody responses irrespective of anti-cancer treatment status. A cellular response was detectable in 63% of the participants after two doses, and no correlation was observed with anti-cancer treatment status or antibody response (Fig. 1b). Administration of a third vaccine dose increased humoral responses in 92% of participants who had not received antibody to the B cell–specific surface antigen CD20 (anti-CD20) in the previous 12 months, in contrast to 17% of those who had (Fig. 1c). People with indolent B-NHL also had improved humoral responses after the third dose, but a third of the participants continued to have relatively low antibody levels (<100 BAU/ml). Binding of the vaccine-induced antibodies to the Omicron variant was three- to fourfold lower than their binding to the wild-type Wuhan strain (Fig. 1d). A good correlation was observed between the binding of these antibodies to the wild-type strain and to variants of concern; thus, binding to each variant can be predicted from binding to the wild-type strain.

The implications

The UK PROSECO study shows that the third vaccine dose improves humoral and cellular responses in people with lymphoma. However, despite this, after three doses, a substantial proportion of those with indolent B-NHL continue to have lower antibody levels than those in healthy donors. This finding emphasizes the urgent need for antibody monitoring to guide the timing and number of doses required in these people, perhaps using 'normal ranges' in healthy people as a threshold. Extended revaccination strategies should also be implemented for those who were vaccinated while on active anti-cancer therapy, especially anti-CD20.

Our study has several limitations. Its observational nature meant that the study had to be pragmatically designed, and peripheral blood sampling was not as complete as intended. Thus, immune responses immediately prior to vaccination were not assessed, and information on the durability of responses was lacking. We also did not directly assess the ability of the antibodies to neutralize virus. However, there was a good correlation between ACE2 receptor–blocking activity and pseudovirus-neutralization efficiency in an earlier study[5]. We observed a good agreement between antibody level and ACE2 receptor blocking, which suggests that the antibodies induced in people with lymphoma are functionally similar to those in healthy donors.

The most important question for the immunosuppressed community now is whether there is a correlation between humoral and cellular responses and the risk of infection, hospitalization and death from COVID-19 in patients. To this end, we aim to embark on a detailed analysis of the clinical outcomes of COVID-19-infected participants in the UK PROSECO study.

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EXPERT OPINION

"The authors' extended analysis of serological, cellular and pseudoneutralization responses in a large cohort of patients with lymphoma after SARS-CoV-2 vaccination demonstrates that the strongest predictor of antibody response is the time between vaccination and treatment, regardless of the number of vaccine doses administered. Importantly, they make the novel observation of anti-spike T cell responses regardless of treatment and provide guidance regarding additional vaccine doses or alternative strategies in this patient cohort." **Ailong Huang, Chongqing Medical University, Chongqing, China.**

FIGURE

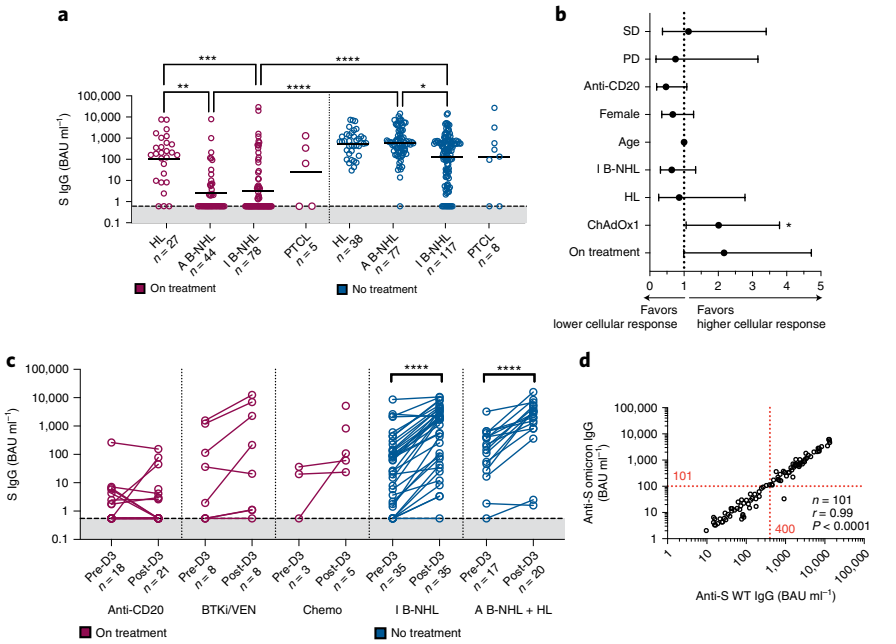

Fig. 1 | Immune responses after SARS-CoV-2 vaccination. a, Antibody levels after two vaccine doses in Hodgkin lymphoma (HL), aggressive B-NHL (A B-NHL), indolent B-NHL (I B-NHL) and peripheral T cell lymphoma (PTCL), with (red) or without (blue) systemic therapy. S IgG, anti-spike immunoglobulin G; BAU, binding antibody units. *$P = 0.0288$, **$P = 0.0008$, ***$P = 0.0004$ and ****$P < 0.0001$. **b**, Multivariable analysis of factors behind cellular responses after two vaccine doses. SD, stable disease; PD, progressive disease; On treatment, active anti-cancer treatment. **c**, Antibody responses before (Pre-D3) and after (Post-D3) three vaccine doses. BTKi/VEN, BTK inhibitor plus venetoclax; Chemo, chemotherapy. ****$P < 0.0001$. **d**, Correlation between binding of anti-S to Omicron and to the wild-type (WT) strain.

BEHIND THE PAPER

The UK government initiated a national SARS-CoV-2 vaccination program in mid-December 2020. We immediately questioned whether vaccination would protect immunosuppressed people, such as those with lymphoma, from COVID-19 disease, and whether any clinical or laboratory markers could be used to predict immune responses. For a complete analysis, we realized we needed to collect pre-vaccination blood samples and we needed a sample size that was adequately powered to control for confounding factors that might contribute to an impaired immune response. So, we set out to rapidly design and begin a clinical trial in a race against the national vaccination program, with no guarantee of securing funding. What we had aplenty was a dedicated team of scientists, nurses, doctors and highly altruistic patients who recognized the importance of the questions being asked. In April 2021, the Blood Cancer UK Vaccine Consortium provided us with the funding that enabled us to continue our study. **S.H.L.**

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This paper reports a good correlation between the ACE2 receptor–blocking activity of anti-S antibodies (measured in our study) and the extent of pseudovirus neutralization.

FROM THE EDITOR

"This work by Lim and colleagues stood out because it characterizes the cellular and humoral immune responses to SARS-CoV-2, including variants of concern, in the largest cohort of patients with hematological malignancies so far, and after different vaccination doses and anti-cancer treatments. Previous observations relied on smaller and more heterogeneous cohorts, and these findings may help guide and prioritize vaccination schedules and close monitoring of COVID-19 outcomes in this fragile population." **Editorial Team, *Nature Cancer***