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Letter

Anti-spike antibody response to SARS-CoV-2 booster vaccination in patients with B cell-derived hematologic malignancies

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It has been reported that ~15%–25% of patients with hematologic malignancies fail to make anti-spike (anti-S) antibodies in response to full dosing of SARS-CoV-2 mRNA vaccines (Greenberger et al., 2021; Griffiths and Segal, 2021). Patients with B cell malignancies are at the highest risk of not making anti-S antibodies. Although the complete immune response in B and T cells is not fully understood, these findings suggest that seronegative patients may be vulnerable to breakthrough infections. Patients with B cell malignancies are of particular concern because, in the pre-vaccine period of the pandemic, some patients with blood cancer who contracted COVID-19 had prolonged, severe infections; generated variant strains (Corey et al., 2021); and demonstrated significantly higher mortality rates compared to the general population (Bakouny et al., 2020; Vijenthira et al., 2020).

In a recent placebo-controlled trial, booster vaccination mediated an increase of anti-S antibodies and neutralizing antibodies in immunosuppressed patients who had solid organ transplantation (Hall et al., 2021). On August 12, 2021, the U.S. Food and Drug Administration (FDA) amended the emergency use authorization for the mRNA vaccines (BNT162b2 and mRNA-1273) to allow the use of a booster dose for immunocompromised people. We report here the antibody responses to booster vaccination obtained prior to FDA authorization in 49 patients with B cell-derived hematologic malignancies.

As described previously (Greenberger et al., 2021), we used a prospective national registry (The Leukemia & Lymphoma Society National Registry; https://www.ciitizen.com/lls/; NCT04794387) to assess the serologic response to vaccinations against SARS-CoV-2. The semiquantitative Elecsys Anti-SARS-CoV-2 S enzyme immunoassay (Roche) for the detection of IgG anti-S1-RBD-SARS-CoV-2 was used with a positive cutoff of at least 0.8 AU/mL and a maximum range of 2,500 AU/mL. These assay readouts correlate with neutralizing immunity mediated by vaccination (Resman Rus et al., 2021). It has also been shown recently that both the semiquantitative anti-S antibody and neutralizing levels are inversely correlated with the risk of COVID-19 infections using data from a 30,000-patient trial with the mRNA-1273 SARS-CoV-2 vaccine (Gilbert et al., 2021).

An assessment of anti-S antibody levels was done 27 days (median value, range 1–99 days) before and 28 days (median value, range 12–61 days) after the booster vaccination (Figure S1). There were no restrictions on initial or booster vaccine type. Patients who were nucleocapsid positive before or after the booster vaccination were excluded from the analysis. Only patients who had enrolled in the registry prior to booster vaccination were included in this study. This study was approved by the Western Institutional Review Board, and participants provided informed consent electronically.

Our cohort was composed of 49 patients with B cell malignancies: 25 patients with chronic lymphocytic leukemia (CLL), 18 patients with non-Hodgkin Lymphoma (NHL) including 7 patients with Waldenstrom's macroglobulinemia (WM), 4 patients with multiple myeloma (MM), 1 patient with CLL and marginal zone lymphoma, and 1 patient with Epstein-Barrvirus-associated lymphoproliferative disease (Table S1). The average age was 66 years (range 31–80 years). Fifty-seven percent were male, and 91% were Caucasian. Forty-eight patients initially received the full dosing of the mRNA vaccines (BNT162b2 and mRNA-1273), and 1 patient initially received the recombinant vaccine, Ad26.COV2.S. Thirty-eight patients (78%) were seronegative prior to booster vaccination. Seven patients had low levels of antibodies (<100 AU/mL), and 4 patients had an antibody response (^{3} > 100 AU/mL) prior to booster vaccination. Heterologous and homologous booster vaccines were used in 67% and 33% of patients, respectively. Most patients received boosters in June and July 2021.

Among the total 49 patients, 17 patients (35%) were non-responders, who were seronegative after initial vaccination and demonstrated no change in antibody level after the booster vaccination. Of the 32 patients (65%) that demonstrated an increase in antibody level after the booster vaccination, patients were categorized as seroconverted (21 patients) or sero-elevated (11 patients) (Table S1). The patients in the seroconversion group were seronegative after initial vaccination and demonstrated an increase in antibody level after the booster vaccination, and the median increase in antibody level was 23.1 AU/mL (interquartile range 8.6–623) with a nearly even bimodal distribution divided between low-level and robust responders (2.2–23.1 AU/mL and 125–2,500 AU/mL). The patients in the sero-elevation group were seropositive (^{3} > 0.8 AU/mL) after initial vaccination and demonstrated an increase in antibody level after the booster vaccination, and the median increase in antibody was

2,128 AU/mL (interquartile range, 563.5–1,458.5 AU/mL).

Although examining subgroupings stratified by disease type or malignancy-targeted therapies was not the primary focus, our previous findings suggest that both disease and therapies can affect the serological response to vaccination (Greenberger et al., 2021). Among the 12 patients who received no malignancy-targeted treatments in the past 2 years, only 1 patient (#14) was a non-responder, 7 patients (#23, #26, #28, #29, #33, #34, and #37) demonstrated seroconversion, and 4 patients (#44, #45, #47, and #48) demonstrated sero-elevation. In contrast, among the 21 patients who completed therapy with anti-CD20 antibodies either alone or in combination with other therapies, 12 patients were non-responders, 7 patients demonstrated seroconversion, and 2 patients demonstrated sero-elevation. Notably, 5 of the 7 patients who completed therapy with anti-CD20 antibodies alone or in combination with chemotherapy at least 7 months prior to the booster vaccination demonstrated seroconversion (patients #22, #25, #27, and #32) or sero-elevation (patient #40). In contrast, many of the patients who recently had, or are maintained on, anti-CD20 antibody therapy prior to booster vaccination failed to seroconvert after booster vaccination. It has previously been reported that recovery of B cells begins 6–9 months after rituximab therapy (McLaughlin et al., 1998). Thus, these data suggest that recent treatment regimens containing anti-CD20 antibodies may suppress the response to booster vaccination.

The use of a Bruton tyrosine kinase inhibitor (BTKi) has been shown to be correlated with a lack of response to vaccination (Greenberger et al., 2021; Griffiths and Segal, 2021). Among the patients who experienced sero-elevation and were treated with a BTKi, 2 patients (#43 and #49) discontinued BTKi therapy 7–23 months prior to booster vaccination, 1 patient (#41) maintained a low dose of ibrutinib prior to booster vaccination, and 1 patient (#42) maintained BTKi therapy continuously before and after the booster vaccination. In addition, the 2 patients (#36 and #38) who experienced marked seroconversion after booster vaccination (an increase of over 1,000 AU/mL) stopped BTKi therapy at least 4 months before the booster vaccination. In comparison, 5 patients (#18, #19, #20, #21, and #24) who had very weak seroconversion (an increase of 2.2–5.2 AU/mL) and 2 patients (#30 and #31) who had moderate seroconversion (an increase of 157 and 233 AU/mL) maintained BTKi therapy during booster vaccination. While patients that did not respond to booster vaccination were maintained on BTKi therapy, one exception (patient #10) discontinued BTKi therapy at least 5 months before the booster vaccination but also had prior therapy with obinutuzumab. These data suggest that BTKi therapy can interfere with a response to booster vaccination.

In this small cohort, the immunogenicity of booster vaccination did not appear to be affected by disease type, vaccine type (BNT162b2, mRNA-1273, or Ad26.COV2.S), vaccination pairing (homologous or heterologous), or other malignancy-target therapies (intravenous immunoglobulin, chemotherapy, or hematopoietic stem cell transplantation). However, this cohort was likely not powered to detect differences between these subgroupings.

This limited observational study shows that 55% (21/38) of patients with B cell malignancies who failed to make anti-S antibodies after full SARS-CoV-2 vaccines seroconverted after booster vaccination. The inability to make anti-S antibodies to the booster vaccination was correlated with anti-CD20 antibody therapy, particularly in the past 6 months prior to vaccination. It is encouraging that 7 patients (#19, #20, #24, #30, #31, #41, and #42) maintained on a BTKi seroconverted or experienced sero-elevation after booster vaccination and is consistent with a previous report on one patient (Hill et al., 2021).

There are important limitations of this study. First, the treatment and disease were reported by the patient. We are currently obtaining electronic health care records to verify these reports, which will allow us to provide clarity on exactly when treatments occurred and what the sequence of treatments was. Second, larger studies, especially in well-controlled clinical trials in patients with hematologic malignancies, are needed (two are already underway) to verify these results and understand if and when booster vaccines are most likely to benefit patients on B cell-suppressive therapies. Third, we did not measure neutralizing antibody responses, particularly to the delta variant, B cell memory, or T cell responses.

We conclude that some patients with hematologic malignancies who are seronegative after a full course of vaccination may benefit from a booster. However, regulators, patients, and health care providers should be aware that a sizeable subset of patients with blood cancer may remain at risk of breakthrough COVID-19 infections after full vaccination followed by booster vaccination.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.09.001.

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