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Letter

Efficacy of booster doses in augmenting waning immune responses to COVID-19 vaccine in patients with cancer

Lauren C. Shapiro,[1,6] Astha Thakkar,[1,6] Sean T. Campbell,[2] Stefanie K. Forest,[2] Kith Pradhan,[1] Jesus D. Gonzalez-Lugo,[1] Ryann Quinn,[1] Tushar D. Bhagat,[1] Gaurav S. Choudhary,[1] Margaret McCort,[3] R. Alejandro Sica,[1] Mendel Goldfinger,[1] Swati Goel,[1] Jesus D. Anampa,[1] David Levitz,[1] Ariel Fromowitz,[1] Akash Pradip Shah,[1] Charlotte Sklow,[1] Gregory Alfieri,[1] Andrew Racine,[4] Lucia Wolgast,[2] Lee Greenberger,[5] Amit Verma,[1,*] and Balazs Halmos[1,*]

[1]Department of Oncology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY 10461, USA
[2]Department of Pathology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY 10461, USA
[3]Division of Infectious Diseases, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY 10461, USA
[4]Department of Pediatrics, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY 10461, USA
[5]The Leukemia & Lymphoma Society, Rye Brook, NY, USA
[6]These authors contributed equally
*Correspondence: amit.verma@einsteinmed.org (A.V.), bahalmos@montefiore.org (B.H.)
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We and others have shown the significant impact of COVID-19 infection among patients with a cancer diagnosis, with increased morbidity and mortality with advanced age, co-morbidities, and hematologic malignancies receiving highly immunosuppressive therapies (Mehta et al., 2020). Subsequently, several studies have demonstrated that, following standard COVID-19 vaccinations, most patients with solid tumors develop robust anti-viral immunity as measured by anti-spike IgG antibodies (Addeo et al., 2021; Thakkar et al., 2021). Approximately 20% of patients with hematologic malignancies, however, develop lower seroconversion rates, furthermore patients who had received anti-CD20 antibodies, CAR T cell therapy, and stem cell transplantation (SCT) had the lowest rates post-vaccination (Greenberger et al., 2021a; Thakkar et al., 2021). Since our initial report, there has been increasing interest in waning immunity (Levin et al., 2021), as evident from decreasing IgG levels as well as with reports of breakthrough infections (Mittelman et al., 2021). In August 2021, the FDA authorized "booster" shots (now preferentially called third or additional vaccine doses) for patients who are immunosuppressed. A randomized study demonstrated significant efficacy of such booster vaccinations in solid organ transplant patients (Hall et al., 2021). In addition, population datasets from Israel, where booster dosing has been made available early, highlight both the serological and clinical impact of booster vaccinations for the overall population (Barda et al., 2021). Of particular concern for the vulnerable cancer patient population, a recent small observational study revealed that some patients with hematologic malignancies who were seronegative after a full course of vaccination may benefit from booster vaccination (Greenberger et al., 2021b).

In our current study, we provide follow-up on our original vaccinated cohort with patients who consented for further assessment of anti-COVID-19 immunity (follow-up immunity cohort) and also present data from a single-arm clinical trial where we assessed anti-COVID-19 immunity before and after a "booster" vaccine in patients with a cancer diagnosis (booster vaccine cohort). The primary endpoint was to assess the rate of booster-induced seroconversion among patients who remained seronegative at least 28 days following the standard set of FDA-authorized COVID-19 vaccinations.

Patients who were included in our COVID-19 vaccine studies (Thakkar et al., 2021; Shapiro et al., 2021), who were seen in follow-up during the current study period, were offered a follow-up SARS-CoV-2 spike IgG level 4–6 months after the completion of their primary vaccine series. One hundred and twenty-three patients underwent repeat anti-SARS-CoV-2 spike antibody (S) testing. Of these, 24 patients that were not part of the initial analysis were excluded, and 99 patients were analyzed (Table S1A). Table S1B summarizes the baseline characteristics of this follow-up cohort. No breakthrough COVID-19 infections were reported between completion of the primary vaccine series and follow-up testing. Overall, the initial median anti-S IgG titer was 5,162 AU/mL (mean 14,634, range 50–50,000) after completion of vaccine series and 724.6 AU/mL (mean 6,220, range 50–50,000) at 4–6 months of follow-up ($p < 0.001$). We observed that the majority of patients (34/36, 94% hematologic malignancies; and 55/55, 100% with solid tumors) maintained detectable anti-S IgG titers >50 AU/mL at 4–6 months (Figure S1A). Two patients with hematologic malignancies (multiple myeloma and AL amyloidosis) did not have detectable antibodies at 4–6 month follow-up. Albeit small numbers in the adenoviral vaccine cohort, we observed that patients that had received mRNA vaccination series had a steeper decline in antibody titers compared to those that had received the adenoviral vaccine ($p = 0.03099$) (Figure S1B). The mean change (Δ) for BNT162b2 vaccine was −7,496 AU/mL, whereas the Δ for mRNA-1273 and Ad26.CoV2.S were −11,639 AU/mL and −3,326 AU/mL, respectively.

One hundred and eighty-nine patients with a cancer diagnosis were assessed for enrollment to receive a booster COVID-19 vaccine after at least 28 days following completion of a standard COVID-19 vaccination series. While our study initially offered the BNT126b2 vaccine on study, following FDA/CDC authorization of booster dosing for immunocompromised patients, patients were also permitted to receive the mRNA-1273 vaccine. One hundred and thirty-one patients

met inclusion criteria (Table S1A) and were enrolled in the study via informed-consent process. A cohort of 88 patients underwent anti-S IgG testing pre- and at 4 weeks post-booster vaccination by our analysis cutoff date and are included in the efficacy analysis. The key cohort of seronegative patients also had anti-SARS-CoV-2 T cell response testing pre- and post-booster. The median age of our cohort was 69 years (range 30–91). Fifty-seven patients (65%) had a hematologic malignancy, while 31 patients (35%) had a solid tumor diagnosis (Table S1B). Sixty-four patients (73%) were on active cancer treatment at the time of booster vaccination. Sixty-two patients (70%) received BNT162b2, 22 patients (25%) mRNA-1273, and 4 patients (5%) AD26.COV2.S vaccination prior to booster vaccination, with a median time since last vaccination of 177 days. All patients received a booster vaccination with the vaccine type received at baseline except 8 patients (2 patients received a heterologous BNT162b2, 2 patients a heterologous mRNA-1273, and all 4 AD26.COV2.S patients received heterologous BNT162b2 booster vaccinations).

Among the total 88 patients who received booster vaccinations, 56 patients (64%) were seropositive prior to booster vaccination, and 32 patients (36%) seronegative. Of the 32 seronegative patients, all had hematologic malignancies except for one patient (Table S1B). Our study met its primary endpoint with 18/32 (56%) seronegative patients seroconverting anti-S IgG titers after booster vaccination ($p = 0.000062$) with 14 patients (44%) remaining seronegative. In our cohort, the overall immunogenicity of booster vaccination was affected by disease type with hematologic malignancies having both a statistically significant lower pre-booster antibody response as well as a smaller change in anti-S IgG mean titers post-booster as compared to solid tumors (10,034 versus 22,686 AU/mL, $p = 0.00263$) (Figure S1C). Despite the majority of patients (73%) being on active therapy at the time of booster, even those patients who received therapy within 30 days of booster vaccination had a statistically significant chance for seroconversion ($p = 0.02$). Prior therapy with either a Bruton Tyrosine Kinase inhibitor (BTKi) or anti-CD20 therapy (or both) was also statistically significant for a decrease in both pre- and post-booster antibody seroconversion ($p = 0.01333$) and titer ($p = 0.0000575$). Those patients who received anti-CD20 therapy within 6 months of booster vaccination (Figure S1D) were especially at high risk for reduced seroconversion ($p = 0.04566$).

As most patients in our cohort received BNT162b2 boosters, we were not powered to uncover significant differences in post-vaccination titers between vaccine types, although surprisingly there appeared to be quantitatively higher mean titers after booster vaccination with initial mRNA-1273 or Ad26.CoV2.S vaccination (25,523 and 23,141 AU/mL) as compared to BNT162b2 vaccination (14,829 AU/mL) as well as higher mean titers after mRNA-1273 booster as compared to BNT162b2 (23,948 versus 15,858 AU/mL) (Figure S1E).

Our study cohort also included a subset of patients with known prior COVID-19 infection ($n = 7$). These patients, as anticipated, showed more robust vaccine responses both after standard and booster vaccinations (Figure S1F). Lastly, our study included a unique cohort of patients ($n = 28$) who were tested for anti-S IgG titers at post-initial vaccination, pre-booster and post-booster time points. This representative cohort highlights significant waning of anti-COVID-19 immunity 4–6 months post-vaccination that can be rescued to above pre-vaccination titers after booster vaccination (Figure S1G), suggesting benefit to booster vaccination in the majority of patients with cancer.

Of the patients remaining seronegative after the booster, all had B cell malignancies: 6 patients had chronic lymphocytic leukemia (CLL), 3 patients had Waldenstrom's macroglobulinemia (WM), 2 patients had multiple myeloma (MM), 1 patient had diffuse large B cell lymphoma (DLBCL), and 1 patient each had Mantle Cell and Marginal Zone lymphoma (Table S1C). Of the 32 seronegative patients prior to booster vaccination, 27 patients (84%) had evaluable anti-SARS-CoV-2 T cell response assays at baseline. Of these 27 patients, 20 (63%) had detectable anti-SARS-CoV-2 T cell responses prior to booster vaccination despite a negative antibody response (median 577 mIU/mL, range 133 to >1,800) (Figure S1H). Of the 14 patients who remained seronegative post-booster vaccination, 10 (71%) had evaluable anti-SARS-CoV-2 T cell responses post-vaccination, with 8 patients (80%) having detectable anti-SARS-CoV-2 T cell responses (median 1,146 mIU/mL, range 1,193 to >1,800), only one of which had no baseline detectable T cell response. For those that remained seronegative after booster vaccination, 57% (8/14) were on active therapy at time of booster, with one CLL patient never having received prior therapy. Within the seronegative cohort alone, significantly lower seroconversion rates were seen in those patients treated with prior or current anti-CD20 therapies ($p = 0.042$), with a median time since last anti-CD20 therapy of 3.9 months. Other common prior or current therapies received included cytotoxic chemotherapy (10/14), BTKi (6/14), CAR T therapy (2/14), and autologous SCT (2/14), although sample size likely limits further conclusions.

In conclusion, our results suggest excellent potentiation of anti-COVID-19 immunity with additional dosing of COVID-19 vaccine in patients with cancer.

Even more importantly, our results clearly show a high, more than 50% seroconversion rate along with corresponding stimulation of measurable anti-SARS-CoV-2 T cell activity among the most vulnerable patient cohort, i.e., patients with no detectable immunity following standard vaccinations, calling for broad efforts to provide third vaccinations to such patients. However, our results also demonstrate that some patients will not have a serological immune response to a third mRNA vaccine dose, highlighting the need for continued efforts to develop valid laboratory correlates of anti-COVID-19 immunity and specific studies assessing the potential benefit of subsequent homologous vaccine doses, heterologous vaccinations, passive immunizations, and other unique approaches for these patients.

In addition, our study finds significant waning of anti-COVID-19 immunity over 4–6 months post-standard vaccination as measured by SARS-CoV-2 spike IgG titers among patients with a cancer diagnosis.

While waning antibody titers are not necessarily associated with risk or severity of breakthrough infections, population-based studies in the case of COVID-19 do suggest such association.

Of particular concern is our novel finding of complete loss of detectable immunity in some patients, in particular patients with lymphoid malignancies and especially those on anti-CD20 and BTKi therapies. These data provide further impetus for additional dosing alongside passive immunization strategies as well as other research efforts for this vulnerable cohort.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.11.006.

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AUTHOR CONTRIBUTIONS

L.C.S., A.T., A.V., and B.H. conceived and managed the study; J.D.G.-L., R.Q., M.M., R.A.S., M.G., S.G., J.D.A.M., D.L., A.F., A.P.S., C.S., G.A., and L.G. participated in patient recruitment; L.C.S., A.T., J.D.G.-L., R.Q., C.S., and G.A participated in data curation; T.D.B. and G.S.C. participated in laboratory investigations; K.P. oversaw data analyses; A.R. contributed to project administration; S.C., S.F., and L.W. oversaw investigations. All authors contributed to writing the manuscript.

DECLARATION OF INTERESTS

R.A.S. serves as a consultant with Morphosys and Miragen and is on the faculty at Physicians' Education Research. A.V. has received research funding from GlaxoSmithKline, BMS, Janssen, Incyte, MedPacto, Celgene, Novartis, Curis, Prelude, and Eli Lilly and Company; has received compensation as a scientific advisor to Novartis, Stelexis Therapeutics, Acceleron Pharma, and Celgene; and has equity ownership in Stelexis Therapeutics. All other authors declare no competing interests.

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