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Letter

Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma

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COVID-19 mRNA vaccines are highly efficacious in preventing COVID-19 morbidity and mortality in phase 3 clinical studies as well as in real-world settings. Emerging evidence suggests that some individuals with underlying comorbidities may mount suboptimal antibody responses to SARS-CoV-2 immunization (Addeo et al., 2021; Monin et al., 2021; Thakkar et al., 2021). Indeed, patients with multiple myeloma (MM) are immuno-compromised due to defects in humoral and cellular immunity as well as due to immunosuppressive therapy. Preliminary reports indicate that the antibody response in MM after the initial dose of SARS-CoV-2 mRNA vaccine is attenuated and delayed compared to healthy controls (Bird et al., 2021; Terpos et al., 2021). Moreover, MM patients who receive anti-CD38 monoclonal antibodies may have poorer vaccine-induced antibody responses even after completion of the full two-dose mRNA vaccine regimen (Pimpinelli et al., 2021). The kinetics of the vaccine responses in MM patients with prior COVID-19 infection and the impact of treatments, including BCMA-targeting agents, to vaccine response remain unknown.

We analyzed SARS-CoV-2 spike-binding IgG antibody levels in 320 MM patients who received COVID-19 vaccinations in early 2021 (69.1% BNT162b2 by Pfizer-BioNTech, 27.2% mRNA-1273 by Moderna, and 3.8% unknown) through the use of the COVID-SeroKlir Kantaro SARS-CoV-2 IgG test (Amanat et al., 2020). Of these patients, 18.8% (60/320) had COVID-19 prior to immunization. A detailed description of the patients and their clinical MM disease characteristics is presented in Table S1A. Of 320 MM patients, 260 (81.3%) had SARS-CoV-2 spike-binding IgG antibody levels measured at least 10 days after receiving the second vaccine dose (median 51 days, range 11–118 days). Of the fully immunized MM patients, 84.2% (219/260) mounted measurable SARS-CoV-2 spike-binding IgG antibody levels which varied by three orders of magnitude (median 149 AU/mL, range: 5–7,882 AU/mL), and 41 individuals (15.8%) had values below the level of detection (Figure S1A). Vaccine-induced antibody responses in the control group of 67 health care workers selected from an ongoing observational study to best match the MM population were, in comparison, more homogeneous (median 300 AU/mL, range: 21–3,335 AU/mL), and no individuals had antibody levels below the level of detection. Notably, antibody levels in the 38 fully vaccinated MM patients with prior reported COVID-19 infections were 10 times higher than those of MM patients that were naive at the time of vaccination (median for COVID-19 survivors: 801 AU/mL [range: 0–7,882 AU/mL] versus median for COVID-19 naive MM patients: 68.5 AU/mL [range: 0–3,174 AU/mL], $p < 0.001$, Mann-Whitney *U* test). This difference has been described previously for healthy vaccinated individuals (Ebinger et al., 2021; Krammer et al., 2021). Repeat antibody measurements from before the initial vaccination to 60 days after the second vaccination confirm delayed and suboptimal antibody responses, particularly in patients with MM and without prior SARS-CoV-2 infection compared to vaccinated healthy individuals without co-morbidities (Figure S1C).

Patients receiving myeloma treatment had significantly lower SARS-CoV-2 spike-binding IgG antibody levels after two vaccine doses ($p = 0.004$, Mann-Whitney *U* test) compared to patients not receiving anti-myeloma therapy (median antibody level on active therapy: 70 AU/mL, compared to MM patients without active therapy: 183 AU/mL). Looking at treatment categories, we found significantly lower antibody levels for patients receiving anti-CD38-containing regimens ($p < 0.001$) and BCMA-targeted therapy ($p = 0.003$) but not for the other treatments ($p = 0.55$) compared to patients not actively receiving anti-myeloma therapy (Figure S1B).

Of note, 15.8% of the MM patients (41/260) failed to develop any SARS-CoV-2 spike-binding IgG antibodies despite having received both doses of mRNA vaccines. 24/41 (58.5%) of these "non-responders" were on anti-CD38 antibody-containing therapy at the time of vaccination, 13/41 (31.7%) were on anti-BCMA bispecific antibody therapy, and 4/41 (9.8%) had undergone anti-BCMA CAR-T therapy more than three months prior. Univariate analysis showed a significant association of the following disease-related factors with the absence of SARS-CoV-2 spike-binding IgG despite completing the full immunization schedule: more previous lines of treatment (>3 lines, $p = 0.035$ or >5 lines, $p = 0.009$), receiving active MM treatment ($p = 0.005$), grade 3 lymphopenia at time of vaccination ($p = 0.018$), receiving anti-CD38 monoclonal antibody therapy ($p = 0.042$), and receiving BCMA-targeted therapy ($p < 0.001$). Multivariate logistic regression found that, after correcting for age, vaccine type, lines of treatment, time since MM diagnosis, response status, and lymphopenia, anti-CD38-containing treatment ($p = 0.005$, odds ratio [OR] = 4.258) and BCMA-targeted treatment ($p < 0.001$, OR = 10.269) remained significantly associated with the probability of not developing antibodies after vaccination (Table S1A).

The clinical relevance of these observations is further emphasized by the fact that we observed 10 cases of COVID-19 in MM patients after one (n = 7) or both (n = 3, no anti-spike IgG antibodies at the time of infection) doses of the mRNA vaccination (Table S1B). Six patients received outpatient treatment (including infusion of anti-spike monoclonal antibodies in 4/6 patients). However, four of these patients required subsequent hospitalization due to severe COVID-19, and one patient, who had no detectable SARS-CoV-2 spike-binding IgG antibodies >10 days after full vaccination, died after prolonged intubation for hypoxic respiratory failure. None of the other MM patient developed symptoms suggestive of COVID-19 after vaccination with a median follow-up of 122 days (range 13–185 days) after the first dose.

This evidence, taken together, shows that MM patients mount a highly variable antibody response after completing the recommended two-dose COVID-19 vaccination regimen, and 15.8% develop no detectable SARS-CoV-2 spike IgG antibodies. The current analysis represents a real-world, convenience sample in which not all participants were able to give samples for all time points. Of note, the COVID-SeroKlir Kantaro SARS-CoV-2 IgG Ab has a large dynamic range, but some antibody values included were capped at 125 AU/mL for technical reasons. These capped antibody values could potentially mask a bigger difference between MM patients and healthy controls. Only two out of the 260 MM patients shown in Figure S1A had capped test values (>125 AU/mL). It is important to note that the current report focuses on the quantification of spike-binding IgG antibody levels, but determination of virus neutralization, IgG subtype, and T cell immunity is needed in order to fully understand COVID-19-vaccine-induced immune responses in MM patients. These studies are ongoing and will complement the data presented. Follow-up studies will demonstrate the durability of vaccine-induced antibody responses beyond three months after the second vaccine dose. It is possible that individuals that mount low-to-modest antibody responses will "sero-revert" more rapidly than those with very high antibody titers.

Our findings underscore the need for routine serological monitoring of MM patients following COVID-19 vaccination to allow for personalized risk reduction measures in the context of relaxing mask and social distancing mandates for vaccinated individuals. The combination of specific risk factors in the MM population and the potential for cancer-directed therapies to hamper vaccine responses more broadly (Addeo et al., 2021; Thakkar et al., 2021) support the need for clinical trials that assess the use of prophylactic strategies (e.g., monoclonal antibodies) to mitigate SARS-CoV-2 infection risk in patients who are likely to have suboptimal vaccine response as well as studies that explore additional immunization strategies with different vaccine types or booster vaccinations (Werbel et al., 2021).

SUPPLEMENTAL INFORMATION

Supplemental Information can be found online at https://doi.org/10.1016/j.ccell.2021.06.014.

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DECLARATION OF INTERESTS

The Icahn School of Medicine at Mount Sinai has filed patent applications relating to SARS-CoV-2 serological assays and NDV-based SARS-CoV-2 vaccines, and these list Florian Krammer as co-inventor. Viviana Simon and Carlos Cordon-Cardo are listed on the serological assay patent application as co-inventors. Mount Sinai has spun out a company, Kantaro, to market serological tests for SARS-CoV-2. Florian Krammer has consulted for Merck and Pfizer (before 2020) and is currently consulting for Seqirus and Avimex. The Krammer laboratory is collaborating with Pfizer on animal models of SARS-CoV-2. Bo Wang reports consulting fees for Sanofi Genzyme. Ajai Chari reports grants and personal fees from Janssen, Bristol Myers Squibb (Celgene), Amgen, Seattle Genetics, and Millennium Pharmaceuticals/Takeda and personal fees from Karyopharm, Sanofi, Oncopeptides, Antengene, Glaxo Smith Kline, Secura Bio, Shattuck Labs, Genentech, and Abbvie. Florian Krammer reports grants and personal fees from Pfizer and personal fees from Seqirus and Avimex. Sundar Jagannath reports consulting fees for Bristol Myers Squibb (Celgene), Janssen, Karyopharm Therapeutics, Legend Biotech, Sanofi, and Takeda. Samir Parekh reports consulting fees from Foundation Medicine and research funding from Bristol Myers Squibb (Celgene), Karyopharm, and Amgen. Other authors report no relevant conflicts of interest.

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