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Letter

Attenuated response to SARS-CoV-2 vaccine in patients with asymptomatic precursor stages of multiple myeloma and Waldenstrom macroglobulinemia

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Patients with hematologic malignancies, including multiple myeloma (MM) and Waldenstrom macroglobulinemia (WM), experience worse outcomes in response to SARS-CoV-2 infection and exhibit suboptimal responses to vaccination due to humoral and cellular immunity defects and immunosuppressive therapy (Aleman et al., 2021; Greenberger et al., 2021; Griffiths and Segal, 2021). Multiple myeloma (MM) is the second most common hematologic malignancy in the United States and is always preceded by monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM), two precursor conditions that affect approximately 3%–5% of the population over 50 years of age, with African Americans carrying three times the risk (Marinac et al., 2020). More than 10 million individuals in the United States are estimated to have MGUS, and we have previously shown that MGUS and SMM exhibit immune dysregulation (Zavidij et al., 2020). Therefore, we reason that patients with precursor plasma cell dyscrasias may also be at risk for SARS-CoV-2 infection and suboptimal response to vaccination.

We launched the IMmune Profiling with Antibody-based COVID-19 Testing (IMPACT) national cohort study in November 2020 to characterize how the short- and long-term effects of SARS-CoV-2 vaccination are modified by underlying immune dysregulation due to precursor plasma cell dyscrasias. The IMPACT study is a prospective study at Dana-Farber Cancer Institute (DFCI) that enrolled participants from three prospectively followed cohorts: the PCROWD study (NCT02269592), the PROMISE study (NCT03689595), and the CureCloud (NCT03657251) collaborative study with the Multiple Myeloma Research Foundation (MMRF). A questionnaire regarding prior SARS-CoV-2 infection or vaccination was sent to all participants.

Between November 2020 and October 2021, 3,005 individuals completed a questionnaire assessing prior SARS-CoV-2 infection or vaccination (vaccine type and dates of administration). Self-reported data were collected on demographic variables (age, sex, race), diagnosis, past medical history of malignancies, and family history of malignancies. Chart review was conducted to retrieve patient clinical variables, including diagnosis, prior therapeutic interventions, and clinical laboratory test results, including monoclonal protein (M-spike) free light-chain (FLC) ratio, albumin, creatinine, hemoglobin, and bone marrow (BM) plasma cell infiltration percentage. A detailed description of the participants who answered the questionnaire is presented in Table S1A.

Most individuals in our cohort received a full vaccination course (2,771, 92%) (two doses of BNT162b2 or mRNA-1273 or one dose of Ad26.COV2.S), including 269 individuals (8.9%) who received a third dose, while 234 individuals (7.8%) remained unvaccinated. 1,385 (46%) and 1,090 (36%) participants received mRNA vaccines (BNT162b2 or mRNA-1273, respectively), and 145 (4.8%) participants received an adenovirus-vector vaccine (Ad26.COV2.S). SARS-CoV-2 infection was observed in 253 (8.4%) individuals, including 33 (1.1%) individuals who experienced a breakthrough infection after a full vaccination course. Indeed, out of all 974 patients with precursor diseases, 15 (1.5%) patients experienced a breakthrough infection.

To evaluate the humoral immune response, we employed one clinically validated and two research-level SARS-CoV-2 spike protein-binding IgG antibody tests. We used a clinical laboratory improvement amendment (CLIA)-certified antibody test with results returned to patients, including a qualitative test (Quest Diagnostics code #39504), and beginning in March 2021, a semiquantitative test (Quest Diagnostics #34499). On the research level, we used enzyme-linked immunosorbent assays (ELISA) and time-resolved Förster resonance energy transfer (TR-FRET) tests (Supplemental information).

Results for all three tests were available on 261 samples. We compared the results of each assay to the CLIA-certified semi-quantitative test within its quantitative range (1–20 index) (n = 22 samples). The

ELISA results (r = 0.737, p < 0.001), but not the TR-FRET results (r = 0.159, p = 0.481), were significantly correlated with the clinical test results (Figure S1A). Since the TR-FRET assay does not include washing steps while relying on anti-human IgG antibodies to detect anti-SARS-CoV-2 spike protein IgG antibodies, we hypothesized that the increased IgG immunoglobulin levels inherent in plasma cell dyscrasias could interfere with this assay. Further analysis using samples spiked with various concentrations of positive control antibody confirmed that immunoglobulin interference occurred in the TR-FRET assay (Figure S1B). Accordingly, we used antibody titers measured by ELISA for the analysis. We urge providers to be aware of the potential immunoglobulin interferences in immunoassays especially when applied to patients with plasma cell dyscrasias.

We analyzed 1,350 plasma samples from 628 individuals who had received a vaccination, including 201 (32%) individuals with MGUS, 221 (35%) with SMM, 40 (6.4%) with smoldering WM (SWM), 66 (10%) with MM, and 100 (16%) healthy controls (Table S1B). Among them, 547 (87%) individuals submitted at least one blood sample after full vaccination, and 209 (33%) patients submitted multiple samples after a full vaccination course, with a median of 2 (range, 2–6) samples per patient. Patients with SMM were stratified by the 2/20/20 progression risk criteria into low-risk, intermediate-risk, and high-risk groups (Lakshman et al., 2018). While the standard of care for patients with SMM is active monitoring until progression to overt MM, our cohort included 41 (6.5%) SMM patients who have received therapies and 17 (0.3%) SMM patients who were actively treated at the time of blood collection (Table S1C).

To determine factors that contributed to antibody responses to SARS-CoV-2 vaccination, we fit a linear model on antibody titers (Figure S1C and Table S1D). Consistent with previous reports (Bird et al., 2021; Greenberger et al., 2021; Stampfer et al., 2021; Van Oekelen et al., 2021), patients diagnosed with MM were significantly more likely to show attenuated humoral immune response (β −0.44, 95% CI: −0.67, −0.21, p < 0.001). Importantly, patients with asymptomatic SMM had significantly attenuated humoral immune response regardless of their 2/20/20 risk stage, even with low-risk SMM (low-risk: β: −0.22, 95% CI: −0.42, −0.03, p = 0.027; intermediate-risk: β: −0.40, 95% CI: −0.61, −0.19, p < 0.001; and high-risk: β: −0.53, 95% CI: −0.88, −0.18, p = 0.003). A diagnosis of MGUS (β −0.13, 95% CI: −0.28, 0.03, p = 0.103) or SWM (β: −0.15, 95% CI: −0.36, 0.07, p = 0.181) was not significantly associated with attenuated antibody response. However, the coefficients were negative, and we may be underpowered to detect a significant difference for this effect size. Therefore, this result should be interpreted with caution. In addition to disease state, male sex (β: −0.12, 95% CI: −0.22, −0.02, p < 0.010), elapsed time after vaccination (β: −0.00, 95% CI: −0.01, −0.00, p < 0.001), and receiving the BNT162b2 vaccine (β: −0.38, 95% CI: −0.48, −0.29, p < 0.001) were also associated with attenuated antibody response, while SARS-CoV-2 infection prior to vaccination was associated with enhanced antibody response (β: 0.78, 95% CI: 0.58, 0.98, p < 0.001). Collectively, our results indicate that the humoral immune response is attenuated in asymptomatic SMM patients, even those with low-risk SMM and low tumor burden. As we do not screen for SMM, these individuals are largely undiagnosed and would not know that they may be at higher risk for SARS-CoV-2 infection.

Patients with SMM are a heterogeneous population, encompassing patients with indolent MGUS-like disease and patients who will progress to overt MM within 5 years of diagnosis. To determine whether all SMM patients are equally at risk for attenuated humoral immune response, we fit a linear model within the sub-cohort of SMM patients adjusting for clinical variables that are commonly used to monitor the risk of progression in patients with SMM (Figure S1D and Table S1E). We observed that a higher percentage of BM plasma cell infiltration (β: −0.20, 95% CI: −0.37, −0.03, p = 0.018) and a higher FLC ratio (involved/uninvolved light chain, β: −0.16, 95% CI: −0.32, 0.01, p = 0.060), both markers of advanced disease, were associated with lower antibody titers post-vaccination. Prior SARS-CoV-2 infection (β: 0.92, 95% CI: 0.57, 1.27, p < 0.001), receiving the BNT162b2 (β: −0.38, 95% CI: −0.58, −0.18, p < 0.001), and longer elapsed time (β: −0.01, 95% CI: −0.01, −0.00, p < 0.001) after vaccination were again significantly associated with lower antibody response. These results indicate that the more advanced the SMM tumor is, the worse the patient's humoral immune response to SARS-CoV-2 vaccination will be, which may help inform future vaccination strategies in these patients.

While patients with hematologic malignancies are encouraged to receive a third dose of vaccination, we do not have evidence that a third dose may indeed overcome disease-associated immune dysregulation. Therefore, we examined the effect of a third dose of mRNA vaccination on antibody titers in 25 patients (6 MGUS, 10 SMM, 2 SWM, and 7 MM) who received three vaccine doses and submitted blood samples both after the second dose and after the third dose. In these patients, we observed a significant increase in antibody titer after receiving the third dose (paired t test, p = 0.002) (Figure S1E). To determine whether these higher titers could be considered acceptable, we compared patient antibody titers post-third dose (13 MGUS, 12 SMM, 2 SWM, and 31 MM) to those of healthy individuals after the second dose. Since all available samples after the third dose were collected within 65 days post-vaccination (median 33; range, 1–65), we restricted this comparison to samples of healthy individuals collected within 65 days of the second dose of vaccine (median 41; range, 2–64). We observed highly variable antibody titers after the third dose in patients, but, overall, they were comparable to titers post-second dose in healthy individuals (p = 0.833) (Figure S1F). While we do not know how antibody titers post-third dose in patients with plasma cell dyscrasias are compared to titers post-third dose in healthy individuals, our results indicate that this patient population may require one dose more than healthy individuals to reach similar antibody levels. With longer follow-up, we will be able to assess the dynamics of antibody titer waning over time in patients with precursor plasma cell dyscrasias compared to healthy individuals and determine whether the intervals between doses should perhaps be shorter for our patients.

Our model suggested that the humoral immune response in SMM patients with

prior treatment history within 2 years of vaccination was comparable to that of healthy individuals (β: 0.09, 95% CI: −0.09, 0.28, p = 0.311), even though having SMM was a significant predictor of attenuated response (Figure S1C). Indeed, SMM patients with prior treatment history had significantly lower tumor burden than untreated SMM patients in terms of M-spike level ($p < 0.001$) and BM plasma cell infiltration percentage ($p < 0.001$). While early therapy is still under investigation as a strategy in patients with high-risk SMM, these encouraging results suggest that the earlier therapeutic interventions in high-risk SMM patients may effectively downstage SMM patients who may have an improved antibody response to vaccination. Benefits from long-term immunomodulation due to therapy are also possible, but these data need to be evaluated further. In contrast, receiving active treatment for SMM while being vaccinated was near significant as a predictor of attenuated antibody response (β: −0.21, 95% CI: −0.44, 0.02, p = 0.078), consistent with prior reports observed in symptomatic MM (Stampfer et al., 2021; Van Oekelen et al., 2021) (Figure S1C).

Finally, we identified patients who experienced a breakthrough infection after a full vaccination course. Among them, we obtained blood samples from seven patients (2 MGUS, 5 SMM). Their antibody titer after full vaccination, but before infection, (median 1.78, range 1.30–1.83) was comparable to that in healthy individuals after vaccination (p = 0.691). This indicates that factors beyond humoral immune response may contribute to breakthrough infections. We are investigating whether the cellular immune response should also be considered to fully define vaccine-induced immune responses in patients with plasma cell dyscrasias.

In conclusion, our study demonstrates that the humoral immune response to SARS-CoV-2 vaccination is suboptimal, not only in patients with MM and other cancer patients receiving therapy but also in precursor asymptomatic patients, including low-risk SMM. Since early stages of hematologic malignancies were not screened routinely, many individuals who are not currently diagnosed with these precursor conditions may be at risk for an attenuated response to SARS-CoV-2 vaccination and may not be aware of their risk. The third vaccine dose improved their attenuated humoral immune response. Future studies examining whether breakthrough infections are indeed associated with other precursor conditions need to be explored. Providers should be aware that a substantial subset of patients with plasma cell dyscrasias, even if asymptomatic, may be at high risk of breakthrough SARS-CoV-2 infections.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.ccell.2021.12.003.

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DECLARATION OF INTERESTS

E.S.F. is a founder, equity holder, and scientific advisor for Civetta Therapeutics, Jengu Therapeutics (board of directors), and Neomorph Inc. and a consultant to EcoR1 Capital, Sanofi, Deerfield, and Avilar. The Fischer lab receives or has received research funding from Novartis, Astellas, Deerfield, Interline, and Ajax. I.M.G. is a consultant for AbbVie, Adaptive, Bristol Myers Squibb, Celgene Corporation, Cellectar, CohBar, Curio Science, Dava Oncology, Genetech, Huron Consulting, Karyopharm, Magenta Therapeutics, Menarini Silicon Biosystems, Oncopeptides, Pure Tech Health, Sognef, Takeda, and The Binding Site; an advisor for Mind Wrap Medical, LLC; and an advisor and consultant for Amgen, Aptitude Health, GlaxoSmithKline, GNS Healthcare, Janssen, Pfizer, and Sanofi. I.M.G.'s spouse, William Savage, MD, PhD, is CMO and equity holder of Disc Medicine.

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