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RESEARCH LETTERS

Decreased Antibody Responses to Ad26.COV2.S Relative to SARS-CoV-2 mRNA Vaccines in Patients With Inflammatory Bowel Disease

Currently, 3 vaccines have been granted Emergency Use Authorization for coronavirus disease 2019 (COVID-19) prevention in the United States. These include the messenger RNA (mRNA) platform vaccines (mRNA-1273; Moderna/National Institutes of Health) and BNT162b2 (Pfizer-BioNTech) and an adenovirus vector vaccine (Ad26.CoV2.S; Johnson & Johnson), which were 94%, 95%, and 67% effective against COVID-19 infection in their phase III registry trials against the endemic variants at the time, respectively.[1–3] All 3 vaccines target the viral spike (S) protein that facilitates severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into host cells via its receptor binding domain. Although the mRNA platform vaccines are 2-dose vaccines administered 3–4 weeks apart, the Ad26.CoV2.S is administered as a single dose. Another adenovirus vector vaccine (ChAdOx1; Astrazeneca), not yet authorized in the United States, is intended as a 2-dose regimen with an interval of 8–12 weeks.

Patients with inflammatory bowel disease (IBD) on corticosteroids, immunomodulators, and advanced therapies may have normal to slightly decreased humoral responses to the SARS-CoV-2 mRNA vaccine platforms.[1] In addition, patients receiving infliximab and/or thiopurines have significantly lower rates of seroconversion than those on vedolizumab monotherapy after a single dose of either BNT162b2 or ChAdOx1.[2] A study of solid organ transplant recipients showed decreased humoral responses to Ad26.CoV2.S vaccine relative to both mRNA platform vaccines, although it is unknown whether these findings are generalizable to other immune compromised populations.[4] We aimed to assess for differences in serologic responses among patients with IBD who received Ad26.CoV2.S relative to those receiving mRNA-1273 or BNT162b2.

Among 353 vaccine recipients with IBD participating in a prospective nationwide SARS-CoV-2 vaccine registry without prior COVID-19 infection and who had completed a full vaccine regimen, 148 (42%), 193 (55%), and 12 (3%) received mRNA-1273, BNT162b2, and Ad26.CoV2.S, respectively. Demographic and disease characteristics were similar across vaccine groups (mean age, 51 years, 62% were female) (Supplementary Table 1). Approximately 290 (83.1%) participants were on immune-modifying therapies (IMTs), as defined by receipt of advanced therapies (biologics or JAK inhibitors, 80.2%), immunomodulators (16.6%), and/or systemic corticosteroids (6.6%) at the time of initial vaccination. At least 2 weeks after completion of the vaccine regimen, positive antibody levels were detected in 121 (100%), 142 (99%), and 9 (90%) patients receiving mRNA-1273, BNT162b2, and Ad26.CoV2.S, respectively (Figure 1*A*). Quantitative $\log_{10}$ (anti-Spike IgG) levels at both 2 weeks (14–29 days after regimen completion) and 8 weeks (42–84 days after regimen completion) were significantly higher among recipients of mRNA-1273 and BNT162b2 compared with Ad26.CoV2.S (1 weeks: 4.20 vs 3.92 vs 1.96 for mRNA-1273, BNT162b2, and Ad26CoV2.S, respectively; at least 8 weeks: 3.72 vs 3.41 vs 2.65, respectively; $P < .001$ comparing each mRNA vaccine with Ad26.CoV2.S at each time point) (Figure 1*B*). We performed multivariable analysis assessing quantitative antibody levels after weeks 2 and 8 following vaccine regimen completion, adjusting for the independent effects of time between vaccine regimen and blood sampling, vaccine type, and immunosuppression status. At week 2, only vaccine type was associated with antibody levels, with both mRNA-1273 and BNT162b2 having significantly higher levels than Ad26.CoV2.S (mRNA-1273: β, 2.24; 95% confidence interval [CI], 1.80 to 2.68; $P < .00001$; BNT162b2: β, 1.96; 95% CI, 1.52 to 2.40; $P < .00001$). At week 8, vaccine type remained independently associated with antibody levels (mRNA-1273: β, 1.08; 95% CI, 0.63 to 1.53; $P < .00001$; BNT162b2: $\beta = 0.77$; 95% CI, 0.32 to 1.22; $P < .001$). In addition, lower titers were independently associated with both a longer duration between completion of vaccine regimen and blood sampling (β, –0.009; 95% CI, –0.02 to –0.001; $P = .032$), as well as with receipt of IMT (β, –0.308; 95% CI, –0.52 to –0.10; $P = .004$).

We found that positive levels of IgG(S) were achieved in virtually all IBD vaccine recipients regardless of vaccine type and IMT use. This finding is reassuring for patients with IBD, and supports existing literature that the vast majority of patients with IBD, regardless of IMT receipt, achieve positive humoral response to mRNA vaccines.[1,3] However, we also found that recipients of Ad26.CoV2.S had significantly lower antibody levels than recipients of mRNA platform vaccines, independent of IMT use.

In organ transplant recipients, many of whom receive B-cell–depleting therapies, receipt of Ad26.CoV2.S was associated with both lower likelihood of seroconversion, as well as lower quantitative levels compared with mRNA vaccines.[4] One successful strategy employed to boost levels among organ transplant recipients receiving the mRNA vaccine BNT162b2 is administration of a third dose approximately 2 months after the second dose.[5,6] Although

Abbreviations used in this paper: **CI, confidence interval; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; IMT, immune-modifying therapy; mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.**

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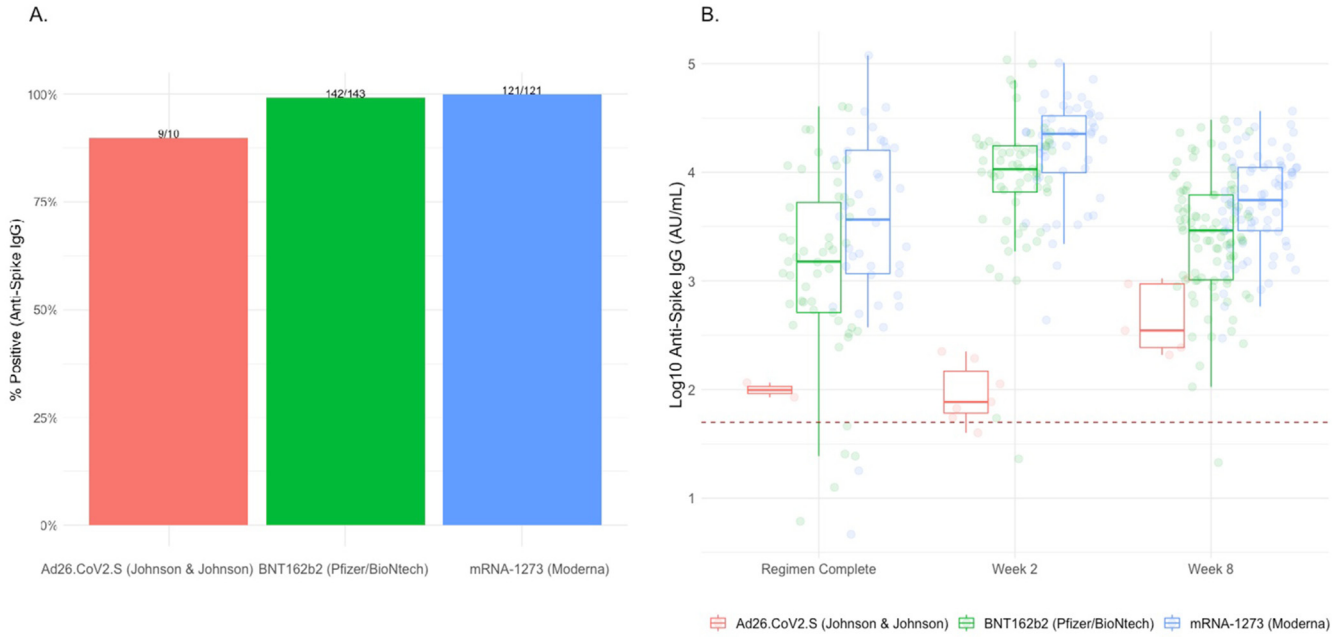

Figure 1. (*A*) Percentage of participants with a positive anti-Spike IgG value (≥50 AU/mL) based on vaccine type at least 2 weeks after regimen completion. (*B*) Log_{10}(anti-spike IgG value) among participants receiving Ad26.CoV2.S (Johnson & Johnson), mRNA-1273 (Moderna/National Institutes of Health), and BNT162b2 (Pfizer-BioNTech) vaccines at 3 time points: after regimen completion (2–13 days after completing regimen), week 2 (14–29 days after completing regimen), and week 8 (42–84 days after completing regimen). *Dotted line* represents manufacturer set anti-spike IgG positivity threshold (>50 AU/mL).

it is reasonable to hypothesize that administration of a booster dose of Ad26.CoV2.S will similarly boost antibody responses among those without positive titers, the rationale for an early booster among those with qualitatively positive but quantitatively low titers is less clear.

The clinical implications of qualitatively positive but quantitatively lower antibody levels among Ad26.CoV2.S recipients are unknown. In a study of 20 Ad26.COV2.S recipients from the COV1001 phase I–IIa clinical trial, neutralizing antibody responses were significantly lower against the B.1.351 and P.1 variants than the original sWA1/2020 strain, but T cell responses and functional non-neutralizing antibody responses were largely preserved.[7] These findings underscore the fact that antibody titers represent only one component of the immune response and that post-vaccination cellular response may be an independent determinant of immunity to SARS-CoV-2. However, it is not known whether lower antibody titers increase susceptibility to SARS-CoV-2 clinical infection; correlations between immune responses and protection from COVID-19 hospitalization and death are needed.

Our findings are limited by a small number of participants receiving Ad26.CoV2.S relative to mRNA-1273 and BNT162b2, as well as a lack of racial and ethnic diversity within the cohort. However, despite the small number of Ad26.CoV2.S recipients, our findings are consistent with other immune compromised populations and have potential clinical ramifications related to the need and timing of booster vaccinations, which are yet to be clarified. Furthermore, our findings highlight the need for data to better understand whether antibody thresholds correlate with protection from clinical infection. Although the clinical implications of positive but low titers are unclear, further comparative effectiveness research of humoral, cellular, and clinical immunity across SARS-CoV2 vaccine platforms is urgently needed to clarify optimal booster vaccine strategies, particularly among immunocompromised patients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2021.08.014.

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Conflicts of interest
These authors disclose the following: Gil Y. Melmed has consulted for AbbVie, Boehringer-Ingelheim, Janssen, Pfizer, Samsung Bioepis, and Takeda, and has received research funding from Pfizer for an unrelated investigator-initiated study. Jonathan Braun has received research funding from Janssen. John Prostko, James L. Stewart, and Edwin C. Frias work for Abbott Diagnostics, a company that performed the serological assays on the biospecimens that were collected for this study. Dermot P. B. McGovern: Pfizer and Takeda. Michael Chiorean: Abbvie, Janssen, Pfizer, and Takeda. Erica Cohen: Abbvie and Pfizer. David Fudman: Pfizer. Caroline Hwang: Abbvie, Janssen, and Pfizer. Donald Lum: Abbvie, Janssen, and Takeda. Ryan McConnell: Abbvie and Pfizer. Nimisha Parekh: Pfizer. Douglas Wolf: Abbvie, Janssen, Pfizer, and Takeda. Bradley Morganstern: Abbvie, Janssen, Pfizer, and Takeda. Sarah Glover: Abbvie, Janssen, and Takeda. Christina Ha: Abbvie, Janssen, and Pfizer. Gaurav Syal: research funding for unrelated investigator study from Pfizer. Corey Siegel: Abbvie, Jannsen, and Pfizer. Adam Ehrlich: Pfizer. Kimia Sobhani: Abbott Diagnostics. The remaining authors disclose no conflicts.

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Supplementary Methods

Adults with Crohn's disease or ulcerative colitis planning to receive or who have already received a SARS-CoV-2 vaccination were enrolled into the Coronavirus Risk Associations and Longitudinal Evaluation-IBD (CORALE-IBD) nationwide registry, as described previously.[7] At the time of enrollment, participants provided demographic information, including age, sex, race, ethnicity, body mass index, IBD type, age at IBD diagnosis, and medication use. On completion of the vaccine regimen (defined as time of receipt of second dose of mRNA vaccine or time of receipt of the single dose of Ad26.COV2.S), whole blood was collected from local participants by venipuncture at 3 different time points: after regimen completion (2–13 days after completing regimen), week 2 (14–29 days after completing regimen), and week 8 (42–84 days after completing regimen). For participants unable to provide in-person samples, whole blood was collected using the TASSO-SST device (Tasso Inc, Seattle, WA) at week 8 only (42–84 days after completing regimen). We analyzed plasma antibodies to the viral spike protein receptor binding domain [IgG(S-RBD)] using the SARS-CoV-2 IgG-II assay (Abbott Labs, Abbott Park, IL) at each time point; IgG(S) $\geq$ 5 0 AU/mL was defined as a positive response. We excluded subjects with a positive antibody value against SARS-CoV-2 nucleocapsid protein ($\geq$ 1.4 AU/mL), indicative of prior COVID-19 infection. We compared the proportions of participants with positive anti-Spike IgG at least 2 weeks ($>$ 14 days but $\leq$ 98 days) after completion of second dose of mRNA vaccines or single dose of adenovirus vaccine (R, version 4.0). We used *t* tests to compare mean log-IgG(S) levels at time of regimen completion, 2 weeks after regimen completion, and 8 weeks after regimen completion across vaccine types. We used multivariable linear regression to adjust for vaccine type, immunosuppressive status (defined as receipt of advanced therapy [biologics or JAK inhibitor], immunomodulators, or corticosteroids at the time of initiation of initial vaccination) and time elapsed between regimen completion and blood sampling. The study protocol was approved by the Cedars-Sinai Institutional Review Board. All study participants provided informed consent.