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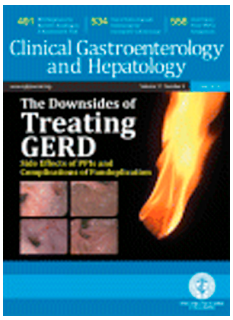

Strong Response to SARS-CoV-2 Vaccine Additional Doses among Patients with Inflammatory Bowel Diseases

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Strong Response to SARS-CoV-2 Vaccine Additional Doses among Patients with Inflammatory Bowel Diseases

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The SARS-CoV-2 pandemic has disrupted health care and has resulted in high mortality rates.[1] Vaccination is an international priority to mitigate the risks of SARS-CoV-2. The initial trials for development of SARS-CoV-2 vaccines excluded individuals with immunocompromising conditions.[2]

As individuals on immunosuppression, including those with inflammatory bowel diseases (IBD), may not mount as robust an antibody titer to vaccination,[3,4] the Food and Drug Administration (FDA) has recommended an additional dose after the initial series.[5]

To date, little is known about the effectiveness and safety of additional vaccine doses in patients with IBD. We sought to quantify the humoral immune response to an additional vaccine in this population.

Partnership to **R**eport **E**ffectiveness of **V**accination in populations **E**xcluded from i**N**itial **T**rials of COVID (PREVENT-COVID) is a prospective, observational, cohort of patients with IBD who have received any SARS-CoV-2 vaccine granted emergency use authorization (EUA) with initial enrollment in March of 2021. Methods for PREVENT-COVID have previously been described.[6] Here we analyzed data on participants who completed baseline and follow-up surveys, had samples obtained 8 weeks following initial vaccination series, and samples 3-8 weeks following an additional vaccine. We excluded those who self-reported prior COVID-19 infection and/or who had positive nucleocapsid assay sat baseline.

Side effects to vaccine were self-reported as none, mild, moderate, severe or very severe. We performed quantitative measurement of anti-receptor binding domain (RBD) IgG antibodies specific to SARS-CoV-2 using the LabCorp Cov2Quant IgG™ assay.[6] Results of 1.0 μg/mL or greater suggest "detectable" serologic response to vaccination and/or prior infection with SARS-CoV-2.

We used descriptive statistics to characterize the population and anti-spike antibody levels before and after additional vaccine and determined the rate of seroconversion among those who were initially undetectable. Variables included age, sex, diseasesubtype, vaccine type (BNT162b2 vs mRNA-1273), time since vaccination, and use of IBD medications. We report median antibody level (interquartile

range, IQR) after initial series, after additional vaccination, and the delta (standard deviation) for each vaccine type. We used Wilcoxon rank sum to compare median change in antibody level with additional SARS-CoV-2 vaccination by detectable response to initial vaccine series. We utilized a linear regression model where quartiles of antibody levels were treated as a continuous variable (1,2,3,4) to determine factors independently associated with level of antibody response. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina). The study protocol was approved by the Institutional Review Board at the University of North Carolina.

A total of 659 participants with IBD were included [415 (63%) initially received BNT162b2 (Pfizer-BioNTech), 243 (37%) initially received mRNA-1273 (NIH-Moderna), and 5 (1%) initially received Ad26.COV2.S (Johnson & Johnson) (supplemental table 1). A total of 408 (98%) of initial BNT162b2 vaccine recipients received an additional dose of BNT162b2, 225 (96%) of initial mRNA-1273 vaccine recipients received an additional dose of mRNA-1273, whereas those that initially received Ad26.COV2.S received additional doses of an mRNA vaccine.

Overall, 612 (93%) had a detectable initial response to SARS-CoV-2 vaccination. Antibody response was measured at a median of 66 days (range 61-73). Following the additional SARS-CoV-2 immunization (median of 48 days, range 43-53) , 99.5% of patients had a detectable antibody titer, including 45/47 (95.7%) of those with undetectable antibodies at the conclusion of the initial series. Both BNT162b2 and mRNA-1273 additional vaccines were associated with a significant increase in titer as compared to baseline ($p<0.001$ for both). On multivariate analysis, mRNA-1273 (beta coefficent 0.38, $p<0.001$) was associated with increased titer and anti-TNF combination therapy (beta coefficient -0.95, $p<0.001$) was associated with reduced titer.

Of the 47 patients with initially undetectable antibodies, the median antibody level after additional dose was 13 ug/mL (IQR 5.8, 24.0) as compared to 51 (IQR 26.0-115.0) for those with detectable antibody after the initial series, $p=0.017$. Change in antibody following the additional dose by vaccine type is

shown in Figure 1, with higher antibody titer after mRNA-1273. Additional vaccination was generally well tolerated in this population, with 44% having no side effects, 24% mild, 25% moderate and 6% severe.

These findings demonstrate substantial immunogenicity to additional doses of SARS-CoV-2 vaccine, even amongst IBD patients with undetectable antibody following the initial series. The highest increase in antibody titer was seen with an additional dose of mRNA-1273. Combination anti-TNF therapy was associated with a significant reduction in antibody titer. Reassuringly, adverse event rates were low among patients receiving an additional vaccination of any type. A recently published series of cancer patients showed 93.7% mounting a detectable humoral vaccine response 2-9 weeks after the initial vaccine series. A third vaccine given to 30 patients with persistently low antibody titers resulted in 88.5% seroconversion rate.[7] In 17 patients with rheumatoid arthritis (RA) who did not mount an initial response to SARS-CoV-2 vaccine, 15 patients reached moderate to maximal post-vaccine titers after additional vaccine. However, in this RA population 16/17 patients held their disease modifying agents prior to the additional vaccine.[8] In our IBD population, 95.7% of those with an initial undetectable response (n=47) developed a detectable humoral response to an additional vaccine, comparable to results in other immunosuppressed populations. Importantly, recommendations in IBD do not include holding immunosuppressive therapies prior to vaccination.[9]

There are a number of strengths to this large prospective study of humoral vaccine response to additional SARS-CoV-2 vaccine in patients with IBD. The cohort is geographically diverse, contributing to generalizability across the US population. The large sample size allows for precise estimates of humoral vaccine response to an additional vaccine dose in patients with IBD. Study limitations include a convenience sample that may not represent the broader US population and the reliance of self-report for details regarding immunization. The relatively low rate of initial undetectable antibody titer makes subgroup analysis difficult to determine independent medication effects of seroconversion with

additional vaccine. Additionally, no threshold has been established for protective immunity in quantitative antibody testing.

Nevertheless, these findings provide urgently needed data regarding the effectiveness of additional mRNA vaccines in immunosuppressed individuals. These data can be used to inform vaccine decisions in patients with IBD.

Figure Legends:

Figure 1: Antibody Change with Additional Vaccination in Patients with Inflammatory Bowel Disease by Vaccine Type (BNT162b2 versus mRNA-1273)

Footer for Figure 1:

- Red diamond represents mean antibody level, green line represents median, the box indicates the interquartile range, the bottom and top lines indicate the lower extreme and upper extreme values (excluding outliers)
- Quantitative measurement of anti-receptor binding domain (RBD) IgG antibodies specific to SARS-CoV-2 were performed using the LabCorp Cov2Quant IgG™ assay
- Dashed line represents results of 1.0 μg/mL; level suggesting serologic response to vaccination
- Results of 1.0 μg/mL (lower limit of quantitation) or greater suggest vaccination and/or prior infection with SARS-CoV-2

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