

Immunogenicity and Safety of Recombinant Herpes Zoster Vaccine in Patients With Inflammatory Bowel Disease on Vedolizumab or Anti-Tumor Necrosis Factor Therapy

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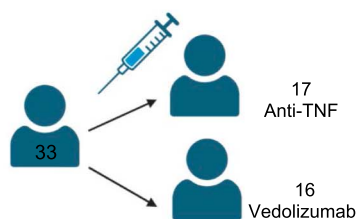
INTRODUCTION: Patients with inflammatory bowel disease (IBD) are at increased risk of herpes zoster and should receive the recombinant herpes zoster vaccine (RZV). We sought to assess the immunogenicity and safety of RZV series in patients receiving anti-tumor necrosis factor (TNF) therapy compared with those receiving vedolizumab.

METHODS: This single-center prospective study enrolled patients with IBD on vedolizumab or anti-TNF monotherapy receiving RZV. Primary outcome assessed cell-mediated immunity (CMI) differences

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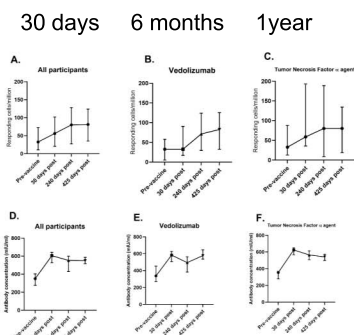
METHODS

Prospective study evaluating RZV vaccine safety and humoral/cell-mediated immunogenicity in patients with IBD at 30 days post-series, 6 months, and 1-year post-immunization.



IMMUNOGENICITY

RZV vaccine demonstrated robust humoral immune response across all biologic therapies at all time points.



SAFETY

Most patients experienced mild transient side effects post vaccination



Vaccination not associated with IBD flares

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between groups postvaccination. Secondary outcomes included humoral response, sustained immunity, and safety monitoring for adverse events and IBD flares. Assessments occurred at baseline, 30, 240, and 425 days postvaccination. Statistical analyses included nonparametric Mann-Whitney *U* tests for between-group comparisons and Wilcoxon signed-rank tests for within-group changes, with significance set at $P < 0.05$.

- RESULTS:** Thirty-three patients enrolled (16 vedolizumab, 17 anti-TNF). CMI responses increased postvaccination in both groups (median 56 cells/million [interquartile range {IQR} 21–102] vs 33 cells/million [IQR 11–73]; $P = 0.13$), with no significant difference between treatment groups. Both groups showed strong antibody responses to vaccination (preimmunization median: 349.9 mIU/mL [IQR 276.8–402.5] vs 90-day median: 605.0 mIU/mL [IQR 525.6–641.0]; $P < 0.001$). CMI responses remained elevated at both day 240 and 425 assessments. Antibody levels remained elevated through day 425 (549.1 mIU/mL, IQR 516.1–585.6), substantially higher than prevaccination levels. No IBD flares occurred; most adverse events were mild and transient.
- DISCUSSION:** RZV demonstrated robust immunogenicity and favorable safety profile in patients with IBD receiving either vedolizumab or anti-TNF therapy. Both cellular and humoral immune responses persisted through 425 days postvaccination.

KEYWORDS: biologic therapy; Crohn's disease; ulcerative colitis; vaccination

ABBREVIATIONS: 5-ASA, 5-aminosalicylic acid; AE, adverse event; Anti-TNF, anti-tumor necrosis factor; CMI, cell-mediated immunity (or cell-mediated immunogenicity); CONSORT, consolidated standards of reporting trials; COVID-19, Coronavirus disease 2019; ELISA, enzyme-linked immunosorbent assay; ELISPOT, enzyme-linked immunospot; HBI, Harvey-Bradshaw index; HZ, herpes zoster; IBD, inflammatory bowel disease; IFN- γ , interferon gamma; IgG, immunoglobulin G; IQR, interquartile range; JAK, janus kinase; mRNA, messenger ribonucleic acid; PBMC, peripheral blood mononuclear cells; RZV, recombinant herpes zoster vaccine (Shingrix); SCCAI, simple clinical colitis activity index; SD, standard deviation; TNF, tumor necrosis factor; VZV, Varicella Zoster Virus

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract that is treated using immune-modifying therapies. These therapies can increase the risk of infections such as reactivation of varicella zoster virus (VZV) in the form of herpes zoster (HZ) (1).

Patients with IBD have been found to have approximately twice the risk of developing HZ compared with the general population, even when not on immune modifying therapy (1–3). This risk is further amplified in patients treated with certain medications, including thiopurines, anti-tumor necrosis factor (TNF) agents, Janus kinase (JAK) inhibitors, and corticosteroids (4,5). A recent systematic review with network meta-analysis evaluating the risk of HZ showed that JAKs, especially with increasing doses, had the highest risk (6). Non-TNF biologics, anti-IL-23 antibodies, and anti-integrin antibodies were not significantly associated with an increased risk of HZ. A recombinant herpes zoster vaccine (RZV) is now available in North America, Europe, and Japan for adults aged 19 years and older with an increased HZ risk. Real-world vaccine effectiveness studies have been limited by cohorts predominantly consisting of patients not receiving biological therapy and short follow-up periods (7,8).

No studies have evaluated whether immune-modifying therapies used to treat IBD affect vaccine-induced immune responses to the RZV series. Studies in other immunosuppressed populations suggest that these individuals may experience a diminished humoral immune response to the RZV series (9). Patients with IBD receiving anti-TNF therapy may have a blunted response to inactivated vaccines, such as influenza, hepatitis B, and pneumococcal

pneumonia (10–13). Studies have shown that vedolizumab does not affect the immunogenicity of influenza and COVID-19 vaccines (10,14). The impact of anti-TNF therapy or vedolizumab on immune responses to the RZV series remains unknown.

We sought to evaluate the VZV-specific cell-mediated immunogenicity (CMI) of an RZV series in patients with IBD receiving anti-TNF therapy compared with those receiving vedolizumab. Our primary outcome was to measure the change in CMI from preimmunization to 1 month after receiving the second dose of vaccine. We hypothesized that patients on vedolizumab would elicit a superior CMI response compared with those on anti-TNF monotherapy. Secondary outcomes included evaluation of sustained CMI at 6 and 12 months postvaccination, assessment of initial and sustained humoral immunogenicity at 1, 6, and 12 months postvaccination, and monitoring the safety profile of RZV in these patient populations.

METHODS

Study design

This prospective, open-label trial evaluated the immune responses to the RZV series in patients with IBD receiving vedolizumab or anti-TNF monotherapy. Participants who presented for routine clinical care at the UW Health Digestive Health Center (Madison, WI) were recruited between May 2019 and July 2023.

Participants

Eligible patients had an established diagnosis of IBD (Crohn's disease or ulcerative colitis) between the ages of 18 and 70 years

and were on stable doses of either anti-TNF monotherapy (maintenance therapy with infliximab every ≤ 8 weeks, monthly golimumab, adalimumab every ≤ 2 weeks, or monthly certolizumab) or vedolizumab monotherapy (maintenance therapy every ≤ 8 weeks) for at least 3 months before enrollment. The exclusion criteria were a known allergy to RZV or its components, any dose of systemic corticosteroid other than budesonide administered within the previous 3 months, concomitant condition requiring immunosuppression for treatment (e.g., rheumatoid arthritis, liver transplant), previous receipt of any HZ vaccine, history of HZ or postherpetic neuralgia within the past year, pregnancy, or receipt of immunoglobulin therapy or blood products within the past year.

Vaccine administration

Shingrix (GlaxoSmithKline), a RZV containing VZV glycoprotein E and the AS01B adjuvant system, was administered as 2 0.5 mL doses intramuscularly into the deltoid region. The second dose was given 2–6 months after the first dose. The vaccine was stored at 2–8 °C and used within 6 hours of reconstitution. Each dose was administered by trained nursing staff according to the manufacturer's specifications.

Study visits and safety monitoring

Study visits included baseline vaccination (day 0), second vaccine dose administration (2–6 months post first dose), post-vaccination follow-up (1 month post second vaccination approximately 30 days post series completion), 6-month follow-up (approximately day 240), and twelve-month follow-up (approximately day 425). Adverse events were monitored through standardized phone calls approximately 2 weeks after each vaccine dose and at each study visit. Serious adverse events were continuously monitored throughout the study period. Disease activity was assessed using validated indices at each visit to monitor for potential IBD flares.

Outcomes

The primary outcome was the difference in VZV specific CMI from baseline to 1 month after receiving the second dose of RZV vaccine between the vedolizumab monotherapy and anti-TNF monotherapy groups.

Secondary outcomes included: (i) sustained change in CMI at 6 and 12 months postimmunization; (ii) change in VZV antibody concentration from baseline to 1 month post series completion, and comparison of VZV antibody concentrations at 6 and 12 months after vaccine administration; and (iii) safety of RZV vaccine series, which included monitoring of solicited adverse events after each vaccine dose, serious adverse events throughout the study period, and rates of IBD flares measured by validated indices at each visit.

Assessment of immunogenicity

VZV-specific CMI was measured using an interferon gamma- γ enzyme-linked immunospot assay (R and D Systems, Minneapolis, MN). For each assay, 200,000 lymphocytes were incubated with VZV antigen (BioRad, Hercules, CA), phytohemagglutinin (positive control, Sigma-Aldrich, St Louis, MO), or media alone (negative control) on interferon antibody-coated plates for 30 hours at 37 °C. Spots were counted using an AID imaging system. The cell count is reported as the number of responding cells per million cells.

Humoral immunity was evaluated using a commercial VZV-specific antibody enzyme-linked immunosorbent assay kit (IBL America, Minneapolis, MN), according to the manufacturer's specifications adjusted to the World Health Organization First International Standard for varicella zoster immunoglobulin 1987 (National Institute for Biological Standards and Control, Hertfordshire, UK), with all samples run in duplicate.

Assessments of reactogenicity and safety

Patients were instructed to contact the study team with fever, chills, or rash. All patients were contacted approximately 12 days after each RZV vaccine to evaluate solicited adverse events by phone script and assess any unsolicited adverse events. Local (injection site pain, redness, swelling) and general adverse events (fever, headache, fatigue, myalgia) were recorded for 7 days after each vaccination, and unsolicited adverse events for 30 days. Events were graded 0–3, with grade 3 defined as preventing normal activity. Grade 4 events were deemed serious adverse events. All local adverse events were considered related to vaccination; other events' relationships were assessed by investigators.

Disease activity assessment

Clinical disease activity was monitored using the Harvey-Bradshaw Index in patients with Crohn's disease and the Simple Clinical Colitis Activity Index in patients with ulcerative colitis. These validated indices were collected at the baseline and at each follow-up visit.

Statistical analysis

Sample size calculations were based on previous studies of vaccine responses in immunosuppressed populations, particularly the data from Rondaan et al. (15) With estimated medians of 7 and 20 responding cells (SD 8 and 12) for the anti-TNF and vedolizumab groups, respectively, 15 participants per group provided 86% power to detect between-group differences, accounting for 20% attrition. The primary analysis compared changes in CMI from baseline to postvaccination between groups using nonparametric Mann-Whitney *U* tests for between-group comparisons and Wilcoxon signed-rank tests for within-group changes. Spearman tests for correlation were done for continuous variables. The safety analyses used descriptive statistics and the Fisher exact tests for between-group comparisons of adverse events. All analyses were conducted using 2-sided tests with $\alpha = 0.05$.

Ethical considerations

This study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board and was registered at ClinicalTrials.gov (NCT03798691). All participants provided written informed consent.

RESULTS

Study participants

Thirty-three participants were enrolled, and 4 were lost to follow-up, with 2 in each group with 30 participants completing the primary end point evaluation at 90 days and 29 completing the 1 year follow-up (Figure 1). Sixteen patients who received vedolizumab monotherapy and 17 patients who received anti-TNF therapy were included. Patients in the anti-TNF group were older, had longer disease duration, a higher proportion of Crohn's disease, and more frequent IBD-related surgeries (Table 1).

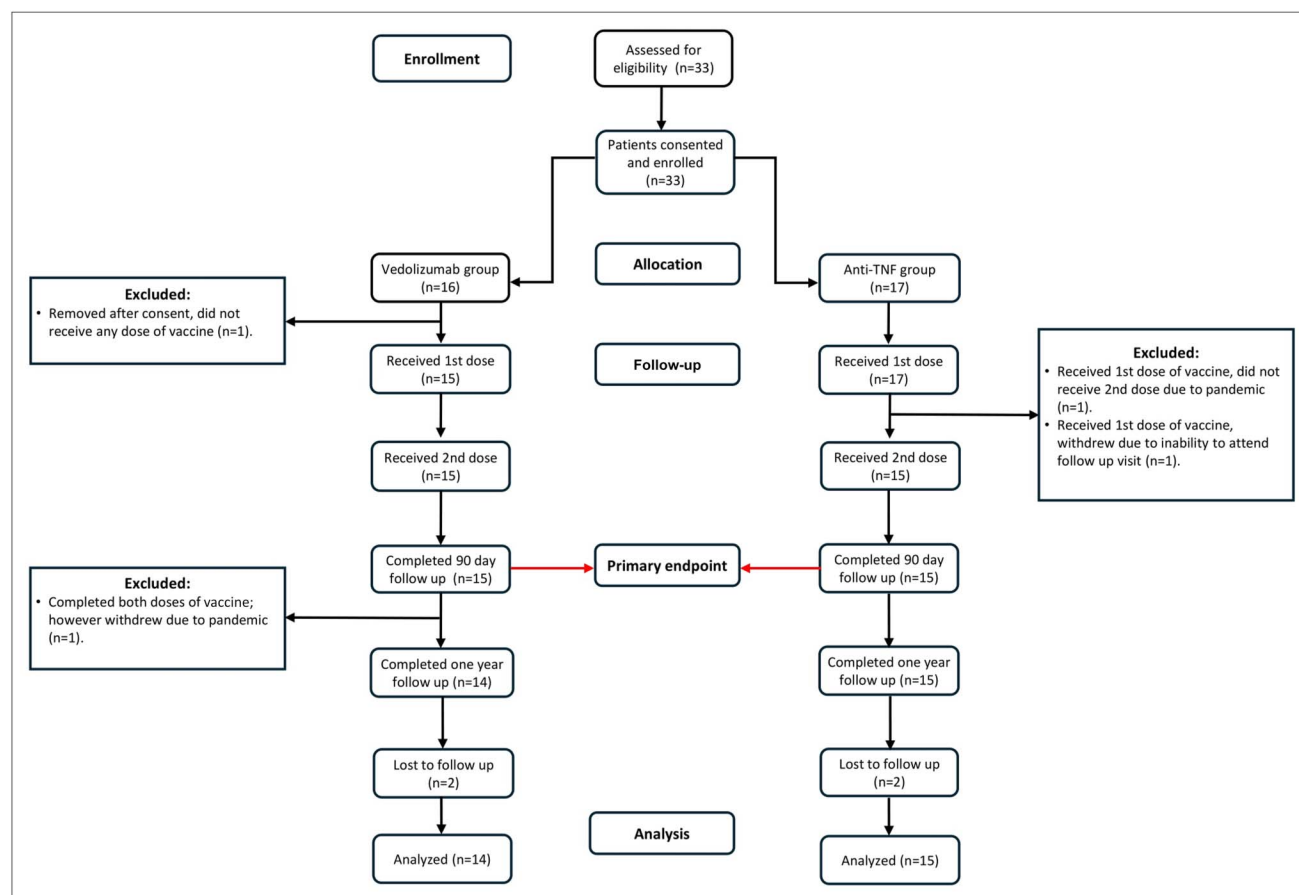


Figure 1. Patient enrollment and study flow. Consolidated Standards of Reporting Trials diagram showing enrollment and follow-up of patients with IBD receiving vedolizumab (n = 16) or anti-TNF (n = 17) monotherapy who received the recombinant zoster vaccine. Four patients were excluded: one before vaccination, one after first dose due to pandemic disruption, one unable to attend follow-up visits, and one who withdrew after completing vaccination. Thirty participants completed the primary end point evaluation at 90 days, with 29 completing the 1-year follow-up. IBD, inflammatory bowel disease; TNF, tumor necrosis factor.

Immunogenicity

Cell-mediated immunogenicity. PMBC samples were available for all participants at the primary end point and 29 at 1 year follow-up, but not all samples were viable for every time point to evaluate VZV-specific CMI on thawing possibly due the length of the study. VZV-specific CMI responses increased after vaccination, although the difference did not reach statistical significance (prevaccine [n = 18] median 33 cells/million, interquartile range [IQR] 11–73 vs postvaccine [n = 24] median 56 cells/million, IQR 21–102; $P = 0.13$). No significant differences in post-vaccination CMI responses were observed between patients receiving vedolizumab (n = 10) (median 33 cells/million, IQR 17–91) and those receiving anti-TNF therapy (n = 14) (median 50 cells/million, IQR 36–193; $P = 0.16$), as shown in Figure 2. The median change in CMI response from preimmunization to postimmunization was similar between the vedolizumab group (33 cells/million, IQR 4–58) and the anti-TNF group (58 cells/million, IQR 33–345; $P = 0.12$). (Table 2).

CMI responses remained elevated throughout the follow-up period in both treatment groups. At day 240 postimmunization, the median CMI response was 80 cells/million (IQR 28–128), with no significant differences between vedolizumab (n = 11; 71 cells/million, IQR 29–124) and anti-TNF groups (n = 9; 80 cells/million, IQR 9–189;

$P = 0.89$). At day 425, the median CMI response remained elevated at 81 cells/million (IQR 35–124), but not significantly elevated compared with baseline ($P = 0.06$), with comparable responses between vedolizumab (n = 7; 83 cells/million, IQR 33–125) and anti-TNF groups (n = 9; 80 cells/million, IQR 19–134; $P = 0.78$).

Humoral immunogenicity. Antibody concentrations increased significantly after completion of the RZV series in all participants (n = 29, one participant did not have viable serum at post immunization) (prevaccination median: 349.9 mIU/mL, IQR 276.8–402.5 vs postvaccination median: 605.0 mIU/mL, IQR 525.6–641.0; $P < 0.001$). Both vedolizumab and anti-TNF groups demonstrated robust humoral responses (Figure 2).

No significant differences in antibody concentrations were observed between the vedolizumab and anti-TNF groups at any time point: postvaccination (582.9 vs 624.0 mIU/mL; $P = 0.22$), day 240 (494.0 vs 564.6 mIU/mL; $P = 0.076$), or day 425 (576.8 vs 541.5 mIU/mL; $P = 0.12$). The median change in antibody concentration from preimmunization to postimmunization was 171.1 mIU/mL (IQR 2.0–300.1) in the vedolizumab group (n = 15) compared with 283.1 mIU/mL (IQR 214.3–379.9) in the anti-TNF group (n = 15), with the difference approaching but not reaching statistical significance ($P = 0.070$). (Table 3).

Table 1. Baseline demographic of patients with IBD on vedolizumab or anti-TNF therapy receiving a recombinant herpes zoster vaccine

	Vedolizumab (n = 16)	Anti-TNF (n = 17)	P value
Age in yr median (IQR)	55 (41–65)	62 (54–62)	0.25
Male (%)	7 (44%)	13 (76%)	0.055
Race or ethnicity (%)			
Caucasian	15 (94%)	16 (94%)	0.37
Hispanic	1 (7%)	0 (0%)	
African American	0 (0%)	1 (7%)	
Type of IBD (%)			
Crohn's disease	8 (50%)	14 (82%)	0.049
Smoking status (%)			0.81
Former	4 (25%)	6 (35%)	
Current	1 (6%)	1 (6%)	
Disease activity clinical remission	16 (100%)	17 (100%)	—
HBI score ≤ 4 or SCCAI score $< 2.5^a$			
Current IBD medication (%)			
Adalimumab	—	9 (53%)	—
Infliximab	—	5 (29%)	
Certolizumab	—	3 (18%)	
Vedolizumab	16 (100%)	—	
Sulfasalazine	1 (6%)	0 (0%)	
Previous IBD medications (%)			
Previous anti-TNF ^b	13 (81%)	—	—
5-ASA	12 (75%)	4 (24%)	
Methotrexate or azathioprine	9 (56%)	4 (24%)	
Positive history of herpes zoster (%)	2 (13%)	4 (24%)	0.70
Length of disease, mo; median (IQR)	162 (69–356)	344 (141–476)	0.037
Previous IBD surgery (%)	2 (13%)	12 (71%)	< 0.001
Steroid use in past yr (%)	6/13 (46%)	2/15 (14%)	0.055
Charlson Comorbidity score median (IQR)	1.5 (0–3.75)	3 (1–4)	0.17

IBD, inflammatory bowel disease; IQR, interquartile range; HBI, Harvey-Bradshaw Index; SCCAI, Simple Clinical Colitis Activity Index; TNF, tumor necrosis factor.

^aParticipants were in clinical remission, defined as a HBI score ≤ 4 for Crohn's disease and a SCCAI score < 2.5 for ulcerative colitis.

^bBeing on previous anti-TNF therapy.

As shown in Figure 2, both treatment groups exhibited significant increases in antibody concentrations from preimmunization to 90 days postvaccination. The vedolizumab group (n = 15) showed a significant increase ($P = 0.007$) despite greater variability in baseline concentrations, while the anti-TNF group (n = 14) demonstrated a more uniform response pattern with highly significant increases ($P < 0.0001$).

Importantly, both treatment groups maintained sustained antibody concentrations throughout the follow-up period, with median concentrations at day 425 (549.1 mIU/mL, IQR 516.1–585.6) remaining significantly higher than prevaccination levels ($P < 0.0001$), demonstrating durability of the humoral immune response over 1-year postvaccination (Table 3).

Age did not correlate with either CMI or antibody concentration. In addition, time since IBD diagnosis did not correlate with either outcome (data not shown). We identified no differences in immune responses between patients with Crohn's disease and

ulcerative colitis. As expected, patients with a history of HZ had a smaller change in CMI prevaccine to postvaccine (No HZ median 50 cells/million; IQR 40–345; HZ history median 7.5 cells/million; IQR undefined as n = 3; $P = 0.036$). No differences in antibody concentrations were observed with history of HZ, except at the last visit when those with no history of HZ (n = 15; median 537; IQR 489–580) had lower antibody concentration than those with previous HZ (n = 5; median 590; IQR 553–686; $P = 0.019$).

Safety

The most frequent adverse events were injection-site pain/soreness (63%, 38/60 doses) and fatigue (22%, 13/60 doses), with all adverse events being mild to moderate in severity (grade 1–2) (Figure 3). Comparing first and second doses, local adverse reactions decreased in both treatment groups (anti-TNF: 86%–53%; vedolizumab: 60%–66%), although injection site pain remained the most common adverse event overall. Systemic

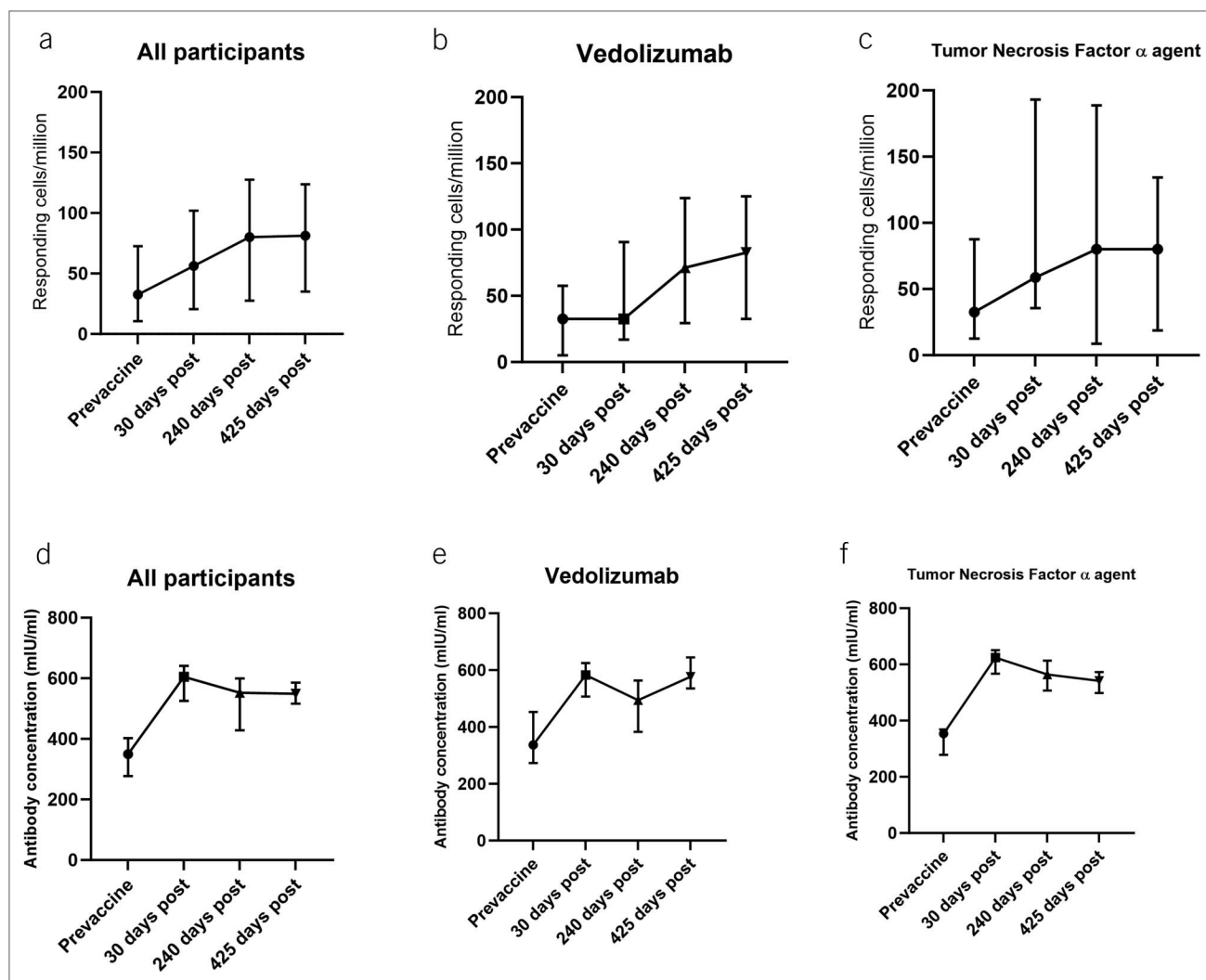


Figure 2. Humoral and cellular immunogenicity of RZV vaccine series in patients with IBD on vedolizumab or anti-TNF monotherapy. Cell-mediated and antibody immune responses were measured before and 30, 240, and 425 days post vaccine series completion. Cell-mediated immune responses at each time point. ELISPOT was used to measure the number of cells that made an interferon-gamma (IFN- γ) response to varicella virus antigen. Antibody responses were measured by ELISA. **(a)** Cell-mediated immune response for all participants. CMI responses increased after vaccination, although the difference did not reach statistical significance (prevaccine [$n = 18$] median 33 cells/million, IQR 11–73 vs postvaccine [$n = 24$] median 56 cells/million, IQR 21–102; $P = 0.13$). **(b)** Cell-mediated immune response for participants treated with vedolizumab. Median number of responding cells was 33 cells/million prevaccine and 1 month postvaccine series. The CMI responses were 71 and 83 cells per million at 240 and 425 days showing sustained responses. **(c)** Cell-mediated immune response for participants treated with anti-TNF- α . Median number of responding cells was 33 cells/million prevaccine and 50 cells/million 1 month post vaccine series. The CMI responses were 80 and 80 cells per million at 240 and 425 days showing sustained responses. **(d)** Antibody responses for all participants. Antibody concentrations increased from baseline (median 349.9 mIU/mL) to 605.0 mIU/mL at 30 days post = vaccine series. The antibody responses were 552.2 and 549.1 mIU/mL at 240 and 425 days showing sustained responses. **(e)** Antibody responses for participants treated with vedolizumab. Antibody concentrations increased from baseline (median 337.0 mIU/mL) to 582.9 mIU/mL ($P = 0.002$) at 30 days postvaccine series. The antibody responses were 494.0 and 576.8 mIU/mL at 240 and 425 days showing sustained responses. **(f)** Antibody responses for participants treated with anti-TNF- α agent. Antibody concentrations increased from baseline (median 353.6 mIU/mL) to 624.0 mIU/mL ($P = 0.001$) at 30 days postvaccine series. The antibody responses were 564.6 and 541.5 mIU/mL at 240 and 425 days showing sustained responses (IQR 278.1–368.8 vs post 624.0; IQR 567.1–651.1; $P = 0.007$ and tumor necrosis factor α agent median antibody concentration pre 337.0 mIU/mL; IQR 273.0–453.3 vs post 582.9 mIU/mL; IQR 507.3–625.2; $P < 0.001$). CMI, cell-mediated immunity; ELISPOT, enzyme-linked immunospot; IBD, inflammatory bowel disease; IQR, interquartile range; RZV, recombinant herpes zoster vaccine; TNF, tumor necrosis factor.

adverse events showed different patterns between groups: anti-TNF recipients maintained consistent systemic reactions across both doses (40% for each dose), while vedolizumab recipients demonstrated increased systemic reactions after dose 2, particularly myalgia/joint pain (21%–50%) and fever/chills (21%–36%). Only one grade 3 adverse event due to fever and myalgias was

reported in one patient on vedolizumab after dose 2, and no IBD flares were reported.

DISCUSSION

In this first prospective study evaluating the safety and immunogenicity of the RZV series in patients with IBD, we demonstrated no

Table 2. Comparison of varicella zoster virus specific cell-mediated immune responses to the recombinant zoster vaccine series

	All participants (cells/million) median (IQR)	P value			Vedolizumab group (cells/ million) median (IQR)	Anti-TNF group (cells/million) median (IQR)	P value ^a
Prevaccine	33 (11–73)	0.13	0.10	0.06	33 (5–58)	33 (13–88)	0.71
1 mo after series completion of 2 dose series	56 (21–102)				33 (17–91)	50 (36–193)	0.16
Change pre to post immunization ^b	43 (23–102)				33 (4–58)	58 (33–345)	0.12
240 d post immunization	80 (28–128)				71 (29–124)	80 (9–189)	0.89
425 d post immunization	81 (35–124)				83 (33–125)	80 (19–134)	0.78

IQR, interquartile range.
^aMann-Whitney *U* test.
^bPost immunization means 1 month after completing 2 dose recombinant zoster vaccine.

difference in VZV-specific CMI in patients on vedolizumab compared with anti-TNF therapy and found that both groups were able to mount and have sustained immune responses. The vaccine series was well tolerated with no serious adverse events and, importantly, was not associated with IBD disease flares. This safety profile is consistent with previous studies of RZV in both immunocompetent and immunocompromised populations. Notably, although previous studies have shown that anti-TNF therapy may attenuate vaccine responses (10), our findings did not support this concern.

Our study did not achieve its primary objective of finding a difference in CMI response between patients on vedolizumab compared with anti-TNF therapy. VZV-specific CMI responses increased after vaccination, although this increase did not reach statistical significance after 1 month. This lack of statistical significance may be attributed to the limited availability of viable cells for CMI evaluation at all time points due to the prolonged duration of the study. Nevertheless, the sustained CMI responses that were measured were maintained up to 1 year post RZV series. In addition, RZV elicited robust initial humoral immune responses in patients with IBD on biologic therapy, with significant increases in antibody concentrations after vaccination in both treatment groups. The humoral immunity generated by RZV vaccination remained remarkably stable throughout the 1-year follow-up period, with antibody concentrations at day 425 still substantially higher than prevaccination levels. These findings contrast with observed patterns of COVID-19 vaccine immunogenicity from previous studies, which demonstrated significant antibody waning at 6 months post third mRNA vaccine dose, particularly in anti-TNF treated patients, along with

modest CMI waning by the same timepoint (14,16,17). This difference likely reflects the fundamentally distinct viral infections and vaccine platforms RZV being a recombinant protein with potent AS01B adjuvant system designed specifically to enhance T-cell responses which are critical for prevention of zoster (18) vs the mRNA technology of COVID-19 vaccines that stimulate vigorous antibody responses and CMI but antibodies may be critical in prevention of infection with CMI support (19). The durability of both humoral and cell-mediated RZV responses regardless of biologic therapy type suggests that RZV may confer more persistent protection against HZ as seen in database studies (20).

Previous studies have evaluated the immunogenicity of RZV in various immunosuppressed populations, with evidence that the immune responses to RZV in immunosuppressed populations are generally lower than those in healthy controls, particularly regarding humoral immunity. However, robust cell-mediated immune responses have been observed across various immunosuppressed groups (9,21–23). Notably, the type of immunosuppression in these populations differs from the targeted immune-modifying therapies used to treat IBD. Two smaller studies have shown preserved vaccine responses in immunomodulating therapy in patients with immune-mediated conditions. Venerito et al evaluated 52 patients with rheumatoid arthritis on rituximab or JAK inhibitors used at lower doses than those typically prescribed for IBD; notably, no patients on anti-TNF therapy, with humoral immune responses assessed only 1-month postimmunization. They demonstrated robust humoral immune responses with significant anti-VZV IgG titer increases

Table 3. Comparison of humoral immune response to recombinant zoster vaccine series

	All participants	<i>P</i> value ^a			Vedolizumab group	Anti-TNF group	<i>P</i> value ^a
Median; interquartile range (IQR)							
Antibody conc mIU/mL ^b prevaccine	349.9 (276.8–402.5)	<0.001	<0.001	<0.001	337.0 (273.0–453.3)	353.6 (278.1–368.8)	0.54
Antibody conc after vaccine 2 dose series	605.0 (525.6–641.0)				582.9 (507.3–625.2)	624.0 (567.1–651.1)	0.22
Antibody conc change pre to post immunization ^c	260.9 (159.9–358.9)				171.1 (2.0–300.1)	283.1 (214.3–379.9)	0.070
Antibody conc 240 d post immunization	552.2 (428.2–599.8)				494.0 (382.7–563.5)	564.6 (506.7–613.7)	0.076
Antibody conc 425 d post immunization	549.1 (516.1–585.6)				576.8 (535.8–645.2)	541.5 (498.2–573.2)	0.12

^aMann-Whitney *U* test.

^bAntibody conc. = antibody concentration in mIU/mL.

^cPost immunization means 1 month after completing 2 dose recombinant zoster vaccine.

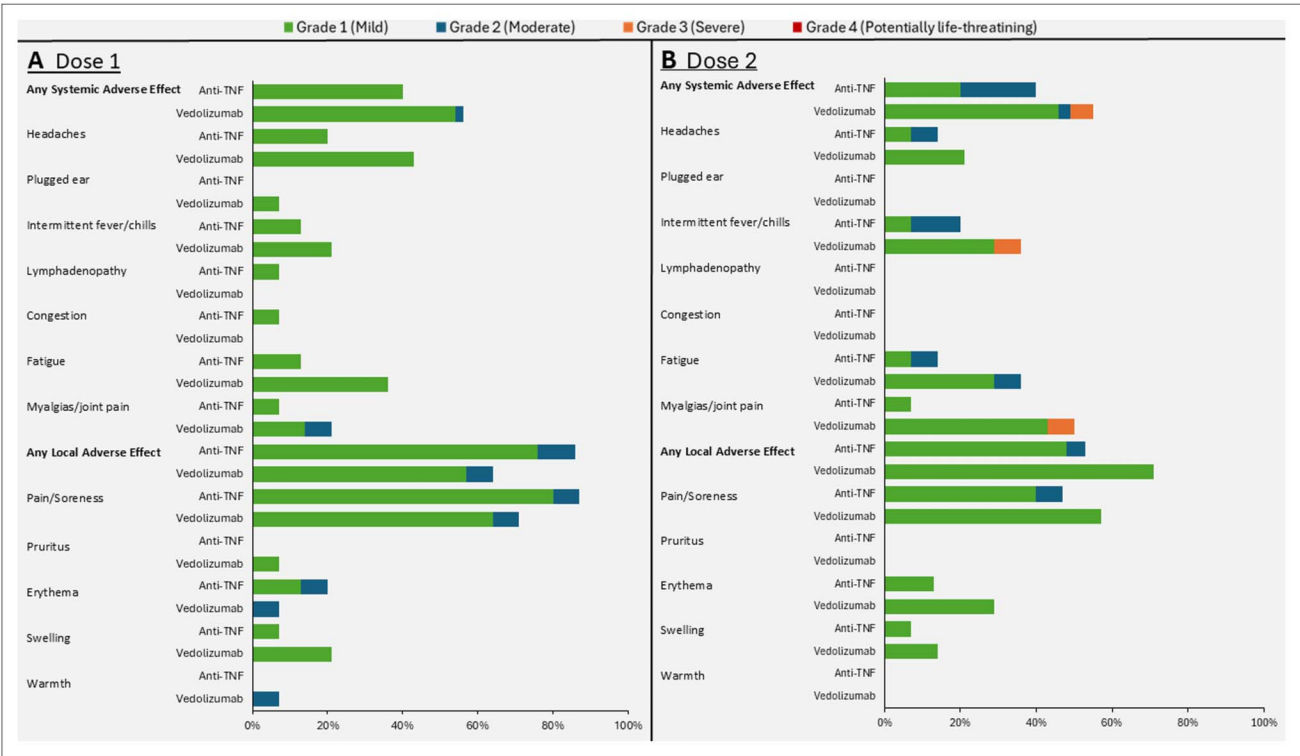


Figure 3. Adverse events after RZV vaccination in patients with IBD on biologic therapy. The figure compares adverse event profiles between patients with IBD receiving vedolizumab or anti-TNF monotherapy after Shingrix (RZV) vaccination. (a) (dose 1) and (b) (dose 2) display the percentage of participants experiencing local reactions (injection site pain/soreness, pruritus, erythema, swelling, warmth) and systemic effects (headaches, fever/chills, fatigue, myalgias) after each dose, with severity graded from 1 (mild, green) to 4 (potentially life-threatening, red). Local adverse effects were common in both treatment groups, with pain being most frequent. Systemic adverse events were more pronounced after the second dose, particularly in the vedolizumab group. These data are from a prospective trial evaluating RZV immunogenicity in patients with IBD on biologic therapy. IBD, inflammatory bowel disease; RZV, recombinant herpes zoster vaccine; TNF, tumor necrosis factor.

after vaccination (24). Similarly, Esteban-Vazquez et al (25) reported adequate anti-gE antibody responses in 49 patients with immune-mediated inflammatory conditions receiving JAK inhibitors at doses lower than used in IBD, also only evaluating responses 1 month postvaccination. Neither study assessed sustained humoral immune response or evaluated CMI. Our study builds on these findings by specifically addressing the population with IBD and comparing 2 therapies with distinct biological mechanisms: gut-selective vedolizumab vs systemic anti-TNF agents demonstrating that RZV remains immunogenic across different immunomodulatory approaches.

Our findings demonstrate the safety and tolerability of RZV in patients with IBD, parallel observations in rheumatoid arthritis and other immunosuppressed populations where vaccination has not been associated with disease flares (24,25). Importantly, we observed no IBD flares after RZV administration, confirming findings from a previous retrospective study evaluating IBD flare rates post-RZV vaccination (26). The vaccine series was well tolerated without any serious adverse events, with most adverse events being mild and only one patient experiencing grade 3 events. This safety profile aligns with studies on RZV in other immunosuppressed populations, including renal transplant recipients, patients with hematological malignancies, and those receiving treatment of solid tumors (9,21–23). These collective findings support the routine administration of RZV in patients with IBD to prevent HZ and its complications, regardless of their biologic therapy.

Our study had several notable strengths. We evaluated both initial and sustained VZV-specific CMI and humoral responses beyond 1 year, providing a comprehensive assessment of RZV immunogenicity. In addition, we directly compared vaccine-induced immune responses between patients on vedolizumab vs anti-TNF therapy, offering insights into how therapies with different biologic mechanisms might impact vaccine response. However, our study had important limitations. The relatively small sample size may have limited our ability to detect differences between the treatment groups. In addition, we did not have a healthy control arm, and our results are limited to patients with IBD on biologic therapy. CMI measurements were constrained by cell viability issues, partly because of extended storage times when the study was paused during the COVID-19 pandemic. We also did not check anti-TNF levels to determine if higher levels correlated with humoral response to RZV. Furthermore, we did not evaluate the immune responses in patients receiving JAK inhibitors, an increasingly important therapeutic class in IBD management.

In conclusion, our findings demonstrate that the RZV series is safe and generates sustained cell-mediated immune and humoral responses in patients with IBD on biologic therapy, supporting current recommendations for RZV vaccination in this population regardless of biologic therapy type. Future studies with larger cohorts, including patients on JAK inhibitors, will be valuable to further validate these findings and explore potential differences in vaccine response across various immune-modifying therapies.

CONFLICTS OF INTEREST

Guarantor of the article: Freddy Caldera, DO, MS, PhD, FACC.
Specific author contributions: F.C.: study concept and design, data analysis and interpretation, manuscript drafting, and critical revision of the manuscript. H.M.: critically revised the manuscript. A.R.A.: critical revision of the manuscript. F.A.F.: critical revision of the manuscript. M.S.H.: data acquisition, critically revised the manuscript.
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Potential competing interests: F.C.: received research support from Takeda Pharmaceuticals, Janssen and Novavax. He has been a consultant for Takeda, Arena Pharmaceuticals, GSK, and Celgene. F.A.F. is a consultant for AbbVie, Avalo Therapeutics, BMS, Braintree Labs, Fresenius Kabi, GI Reviewers, GSK, Iterative Health, Janssen, Pfizer, Sandoz Immunology, Sebela and Viatrix. He previously participated on a DSMB for Lilly Pharmaceuticals. M.S.H.: is a consultant for GSK Vaccines and has received research support from Takeda Pharmaceuticals and Dynavax.

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Study Highlights

WHAT IS KNOWN

- ✓ Patients with inflammatory bowel disease are at increased risk of herpes zoster. The risk is further increased by a certain immune-modifying therapy. A recombinant herpes zoster vaccine (RZV) is now available to reduce the risk of herpes zoster.
- ✓ Previous studies have shown that anti-Tumor necrosis factor may blunt the response to inactivated vaccine such as influenza vaccine.

WHAT IS NEW HERE

- ✓ This is the first prospective evaluating the safety and immunogenicity of an RZV series in patients with inflammatory bowel disease on biologic therapy.
- ✓ Regardless of biologic therapy, the RZV vaccine showed robust humoral immunogenicity. There were no humoral or cell-mediated immunogenicity differences found between vedolizumab vs anti-tumor necrosis factor therapy.
- ✓ Sustained cellular and humoral immunity demonstrated through 425-day follow-up.

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