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ORIGINAL ARTICLE

Safety of Recombinant Zoster Vaccine in Patients with Inflammatory Bowel Disease

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Abstract

Background Patients with inflammatory bowel disease (IBD) are at increased risk of developing herpes zoster. In October 2017, the FDA approved a two-dose adjuvanted, recombinant herpes zoster vaccine (RZV). There is a theoretical concern that vaccine adjuvants may cause flares in patients with immune-mediated diseases. We aimed to assess the rates of IBD flare and adverse reactions after administration of RZV in a cohort of patients with IBD.

Methods We conducted a prospective observational study of patients with IBD who received RZV between February 2018 and July 2019 at a tertiary IBD referral center. IBD activity scores were collected from patients during office visit or phone call after vaccination. The primary outcome was rate of IBD flare, defined as an increase in IBD activity, resulting in escalation of medical therapy, following vaccination. The secondary outcomes were rates of local and systemic adverse reactions after vaccination.

Results We identified 67 patients (28 with ulcerative colitis and 39 with Crohn's disease) who received at least one dose of RZV. The two-dose vaccine series was completed by 55 patients (82%). Median duration of follow-up after vaccination was 207 days. One case of IBD flare was identified. No cases of herpes zoster were identified. Local and systemic adverse reactions were reported in 74.6% and 56.7% of patients, respectively.

Conclusions In this cohort of 67 patients, a low rate of IBD flare (1.5%) was observed after RZV administration. Rates of local and systemic adverse reactions were comparable to those seen in the RZV clinical trials.

Keywords Inflammatory bowel disease · Crohn's disease · Ulcerative colitis · Vaccination · Vaccine adjuvant · Herpes zoster

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Introduction

Characterized by a painful, dermatomal vesicular eruption, herpes zoster (HZ) results from reactivation of latent varicella-zoster virus (VZV) [1]. Patients with inflammatory bowel disease (IBD) are 1.2–1.8 times more likely to develop HZ, compared to patients without IBD [2–4]. In a recent nationwide cohort study, incidence rates of HZ were higher in all age groups of patients with IBD than in the oldest group of patients without IBD [5]. The use of thiopurines, steroids, or anti-TNF agents additionally increases the risk of HZ in patients with IBD [2]. In a recent integrated safety analysis, the use of tofacitinib for ulcerative colitis was associated with an HZ incidence rate of 4.1 (95% CI 3.1–5.2) and was statistically higher with tofacitinib 10 mg twice daily versus placebo [6]. Furthermore, patients with IBD may be at increased risk of developing complications, such as post-herpetic neuralgia, from HZ. In a 2012 clinical review detailing 32 reported cases of HZ in IBD, 7 cases were complicated by involvement of organ systems other than skin, including in 3 cases the central nervous system [7]. Given that patients with IBD are at increased risk of developing HZ and may be at increased risk of subsequent complications, vaccination against HZ in this population is of high clinical importance.

In October 2017, a two-dose recombinant HZ vaccine (RZV; Shingrix) containing recombinant VZV glycoprotein E and $AS01_B$, a liposome-based adjuvant system, was approved by the Food and Drug Administration for prevention of HZ in adults aged ≥ 50 years [8]. In phase III clinical trials, the vaccine demonstrated > 90% efficacy in adults aged ≥ 50 years [9, 10]. Although patients on immunosuppressive medications were excluded from these studies, the vaccine may be of particular importance for patients with IBD on immunosuppressants because unlike the live zoster vaccine (Zostavax), RZV contains inactivated virus. At this time, however, the Advisory Committee on Immunization Practices recommends RZV only in adults aged ≥ 50 years that are immunocompetent or on low-dose immunosuppressant therapy equivalent to < 20 mg/day of prednisone [8].

There is a theoretical concern that vaccine adjuvants such as $AS01_B$ may cause flares in patients with immune-mediated disease [11–13]. Monophosphoryl lipid A, one of two immunostimulants used in $AS01_B$, acts on antigen-presenting cells expressing Toll-like receptor 4, resulting in the production of cytokines and co-stimulatory molecules [14]. In doing so, adjuvants like $AS01_B$ may potentially contribute to immune-mediated disease activity by acting as an environmental trigger of innate immune receptors. However, in a pooled analysis of the phase III trials for RZV, there was no significant difference in relapse rate of pre-existing immune-mediated diseases—including psoriasis, spondyloarthropathy, rheumatoid arthritis, celiac disease, and inflammatory bowel disease—between the vaccine and placebo groups (2.8% in both groups) [15]. These results suggest that despite the adjuvant, RZV may be safe in patients with immune-mediated diseases. To our knowledge, however, the safety of RZV has not been studied specifically in a cohort of patients with IBD. The aim of our study was to assess in a prospective manner the rate of IBD flare as well as adverse reactions after administration of RZV in a cohort of patients with IBD.

Methods

We conducted an IRB-approved prospective observational study among patients with a diagnosis code for Crohn's disease (CD) or ulcerative colitis (UC) and a prescription for RZV. Patients were recruited from Boston Medical Center, a tertiary IBD referral center, from February 2018 to July 2019. Epic Reporting Workbench (Epic Systems Corp., Verona, WI) was used to identify patients that met the inclusion criteria.

Initial data abstracted from electronic medical records included patient demographics, previous and concomitant medications, IBD type and location, and most recent IBD activity score prior to vaccination. IBD activity scores for CD and UC were, respectively, calculated with Harvey Bradshaw Index (HBI) and Simple Clinical Colitis Activity Index (SCCAI) [16, 17]. Patients were monitored for dates of vaccination via local immunization databases at the research site as well as self-report from patients. Patients living in Massachusetts were also monitored for dates of vaccination by querying the Massachusetts Immunization Information System (MIIS), a state-wide web-based immunization registry, every 14 days through the research site's electronic medical record system. Per state law (M.G.L. Chapter 111, Section 24M), all immunizations administered in Massachusetts to any person are required to be reported to the MIIS. IBD activity scores (HBI or SCCAI) and local and systemic reactions were solicited from patients during follow-up office visit or phone call, scheduled approximately 14 days after administration of each dose of RZV in order to capture vaccine-related symptoms within a reasonable time frame. Electronic medical records were also monitored to identify any changes in medical therapy made after vaccination.

The primary outcome was rate of IBD flare following vaccination. IBD flare was defined as an increase in IBD activity score (HBI or SCCAI) resulting in either an increase in dose of any maintenance IBD medication or initiation of a new corticosteroid or biologic medication. The secondary outcomes were rates of local and systemic adverse reactions after vaccination.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Statistical Analyses

Descriptive statistics were used to characterize the population of patients. Data were stored in Microsoft Excel (Microsoft Corp., Redmond, WA) and analyzed using Microsoft Excel and R software version 3.5.3 (R Core Team [2019]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Confidence intervals were calculated using the Clopper-Pearson interval.

Results

A total of 67 patients with IBD (28 with UC and 39 with CD) received at least one dose of RZV. The two-dose vaccine series was completed by 55 of these 67 patients (82%). Baseline characteristics of the cohort are described in Table 1. The median age at the time of first RZV dose administration was 63 (IQR 56–68.5) years. Five patients (7.5%) had a previous history of HZ, and 31 patients (46.3%) had previously received ZVL. Of the 67 patients, 12 (17.9%) were not on any maintenance medications for IBD, 34 (50.7%) were on a single medication, and 21 (31.3%) were on combination therapy. Table 1 also presents the concomitant medications at time of first RZV dose administration. Seven patients (10.4%) were on prednisone, 11 patients (16.4%) were on an immunomodulator (6-mercaptopurine, azathioprine, or methotrexate), 9 patients (13.4%) were on an anti-TNF inhibitor, 15 patients (22.4%) were on vedolizumab, 9 patients (13.4%) were on ustekinumab, and 3 patients (4.5%) were on tofacitinib. The median duration of follow-up after vaccine administration was 207 (IQR 169–304.5) days. No patients developed HZ during the study period. Local and systemic adverse reactions were reported in 74.6% and 56.7% of patients, respectively. Adverse reactions were solicited from patients a median of 21 (IQR 16–32) days after vaccination. Adverse reactions are detailed further in Table 2.

One patient in our cohort experienced an IBD flare after RZV administration. The patient was a 63-year-old man with a history of left-sided UC, no previous history of HZ, and no previous vaccination with ZVL. He was diagnosed with UC 2 years prior and had failed mesalamine, budesonide MMX, infliximab, and prednisone (last taken 29 weeks prior to his first RZV dose). Twenty-two weeks prior to his first RZV dose, he was switched from infliximab to vedolizumab and remained on oral methotrexate due to ongoing symptoms, an elevated fecal calprotectin of 345.1 µg/g, and a colonoscopy showing moderate to severe left-sided UC. Pathology revealed chronic colitis with mild to moderate activity. The patient's UC improved, and two days prior to the first RZV dose, he was noted to be in clinical as well as endoscopic remission (Mayo 1 on flexible sigmoidoscopy). Pathology showed mild architectural changes without active inflammation. The first RZV

Table 1 Clinical and demographic characteristics of cohort

Variable	All patients $N=67$
Age (years) (median, IQR)	63 (56–68.5)
Sex (*N*, %)	
Female	36 (53.7)
Male	31 (46.3)
Race (*N*, %)	
Caucasian	56 (83.6)
African-American	8 (11.9)
Hispanic	1 (1.5)
Asian	1 (1.5)
Other	1 (1.5)
IBD type (*N*, %)	
Ulcerative colitis	28 (41.8)
Proctosigmoiditis	1
Left-sided disease	9
Pancolitis	18
Crohn's disease	39 (58.2)
Ileal	10
Colonic	10
Ileocolonic	19
Duration of IBD (years) (median, IQR)	17 (8–30)
Prior IBD-related surgery (*N*, %)	35 (52.2)
Prior HZ infection (*N*, %)	5 (7.5)
Prior ZVL vaccination (*N*, %)	31 (46.3)
# of failed anti-TNF-α (median, IQR)	0 (0–1)
# of failed biologics (median, IQR)	0 (0–1)
Duration of follow-up (days) (median, IQR)	207 (169–304.5)
Concomitant medications at first dose of recombinant zoster vaccine (*N*, %)	
5-ASA agent	21 (31.3%)
Budesonide	6 (9.0%)
Prednisone	7 (10.4%)
6MP/azathioprine	4 (6.0%)
Methotrexate	7 (10.4%)
Infliximab	4 (6.0%)
Adalimumab	5 (7.5%)
Vedolizumab	15 (22.4%)
Ustekinumab	9 (13.4%)
Tofacitinib	3 (4.5%)

Table 2 Frequency of adverse reactions after recombinant zoster vaccine administration

Variable	Number of patients/total	% (95% CI)
Report of injection-site reaction	50/67	74.6 (62.5–84.5)
Pain	48/67	71.6 (59.3–82.0)
Redness	26/67	38.8 (27.1–51.5)
Swelling	18/67	26.9 (16.8–39.1)
Report of systemic reaction	38/67	56.7 (44.0–68.8)
Myalgia	27/67	40.3 (28.5–53.0)
Fatigue	23/67	34.3 (23.2–46.9)
Headache	20/67	29.9 (19.3–42.3)
Fever	15/67	22.4 (13.1–34.2)
Chills	13/67	19.4 (10.8–30.9)
Nausea	8/67	11.9 (5.3–22.2)

dose was tolerated without disease flare, and the second RZV dose was administered 10 weeks later.

Three days after his second RZV dose, the patient developed recurrent bloody diarrhea with increased stool frequency and urgency. Workup of the patient's symptoms included normal CBC, normal CMP except for mildly elevated alkaline phosphatase at 110 u/L, mildly elevated CRP at 6.2 mg/L, elevated fecal calprotectin at 887.2 µg/g, and negative C Diff toxin PCR. Prednisone was started, and due to a low trough vedolizumab drug level at 7.6 µg/ml without antidrug antibodies, vedolizumab frequency was increased to every 4 weeks. No improvement was seen after 8 additional weeks, prompting a CT enterography and colonoscopy, which confirmed active left-sided UC with moderate to severe chronic active colitis on biopsy. The patient's symptoms were refractory to various additional medical therapies, including a trial of tofacitinib, a prednisone taper, and 3 months of daily subcutaneous IL-2 injections as part of an open-label study. Due to continued symptoms, he underwent a total colectomy with ileostomy 10 months after his second dose of RZV.

Discussion

In this prospective observational study, we monitored patients with IBD for disease flare and for local and systemic reactions after RZV administration. In our cohort of 67 patients, we identified one patient with a 2-year history of ulcerative colitis who developed an IBD flare after administration of his second RZV dose. The patient had previously been on several courses of prednisone and failed multiple maintenance agents (mesalamine, budesonide MMX, and infliximab) but responded to vedolizumab induction and was in clinical and endoscopic remission (Mayo 1) on vedolizumab for 33 weeks before experiencing the flare. The patient tolerated the first dose of RZV but developed recurrent colitis symptoms 3 days after administration of the second RZV dose, ultimately requiring a total colectomy 10 months later due to symptoms refractory to various escalated medical therapies.

One hypothesis that cannot be excluded is that his disease flare may have been induced by a secondary immune response from the second RZV dose. During a secondary immune response, repeat exposure to a previously encountered antigen produces a stronger and faster inflammatory response through activation of B and T lymphocytes and antibodies [18]. Initial sensitization may have occurred from a component of the first RZV dose, and repeat exposure during the second RZV dose may have produced an immune response, resulting in an UC flare. The alternative explanation is that the patient flared in the setting of a low vedolizumab level. Of note, in the GEMINI 1 maintenance study of vedolizumab in UC, approximately 40% of patients with ulcerative colitis who had clinical response to induction were not in clinical remission at week 34 [19].

Our study suggests that rates of IBD flare are not increased by RZV administration. No cases of HZ were identified in our cohort. In this cohort, 74.6% of patients had injection-site reactions, and 56.7% of patients had systemic reactions after RZV administration. These rates are comparable to those observed in the phase III clinical trial of RZV for adults aged ≥ 50 years, where 81.5% of vaccine recipients had injection-site reactions and 66.1% had systemic reactions [9]. Specific types of local and systemic reactions were also observed at rates statistically similar to those seen in the phase III trial, suggesting that patients with IBD are not at higher risk of developing local or systemic reactions after RZV administration.

With the development and use of new adjuvants, multiple vaccines recently approved for clinical use offer greater efficacy than their predecessors. The previously recommended live zoster vaccine (Zostavax) demonstrated a vaccine efficacy of 70% in adults aged 50–59 years, 64% in adults aged 60–69 years, and 38% in adults aged ≥ 70 years [20, 21]. Utilizing the liposome-based $AS01_B$ adjuvant system, however, RZV demonstrated a superior vaccine efficacy of 96.6% in adults aged 50–59 years, 97.4% in adults aged 60–69 years, and 91.3% in adults aged ≥ 70 years [9, 10]. Similar advancements have been seen in hepatitis B vaccines. Three recent phase III clinical trials compared Engerix-B, an existing aluminum-adjuvanted vaccine, to HepB-CpG (Heplisav-B), a new vaccine containing CpG-1018, a novel cytidine-phosphate-guanosine oligodeoxynucleotide adjuvant. Adequate seroprotective levels were achieved in only 65.1–81.3% of patients receiving Engerix-B in comparison with 90.0–95.0% of patients receiving HepB-CpG [22–24]. Given the approval and success of vaccines

containing new adjuvants such as $AS01_B$ and CpG-1018, additional vaccines with novel adjuvants can be expected in the near future.

There is a theoretical concern that by enhancing immune responses to antigens, adjuvants may induce or exacerbate immune-mediated diseases [11–13]. Reports of vaccine-induced immune-mediated disease have been documented in the scientific literature. For example, an increased risk of Guillain–Barré syndrome (GBS) was observed in patients who received the swine influenza vaccine in 1976 [25, 26]. However, subsequent studies of the 2009–2010 influenza season found a smaller-to-insignificant increase in risk of GBS after vaccination [27, 28]. Additionally, the majority of available evidence suggests that immune-mediated disease resulting from adjuvant use is rare [11]. In a pooled analysis of the phase III trials of RZV, 1943 patients with pre-existing immune-mediated disease—including psoriasis, spondyloarthropathy, rheumatoid arthritis, celiac disease, and inflammatory bowel disease—not on immunosuppressive therapy were randomized; the rate of relapse was not increased in the vaccine group (2.8% in both vaccine and placebo groups) [15]. In a recent study of RZV in immunocompromised autologous hematopoietic stem cell transplantation recipients, the rate of immune-mediated diseases was also not increased in the vaccine group (1.4% vs 0.9%) [29]. Our study reinforces this conclusion, as only one case of IBD flare was identified. We postulate that the risk of IBD flare after HepB-CpG is likely low as well, because relative improvements in vaccine efficacy suggest that the CpG-1018 adjuvant in HepB-CpG is less potent than the $AS01_B$ adjuvant in RZV. With the completion of post-licensure surveillance studies, further information on the safety of the RZV and HepB-CpG vaccines will become available.

There were some limitations to our study. First, delays in soliciting adverse reactions may have resulted in lower rates of local and systemic reactions reported by patients. Adverse reactions were planned to be solicited 14 days after RZV administration, but they were obtained a median of 21 days after vaccination in our study due to late reporting of vaccination in certain cases and difficulties in contacting patients. Delays in contacting patients are unlikely to have affected rates of IBD flare in this study, however, because any escalation in medical therapy would have been captured during chart review. Second, the short duration of this prospective study precluded assessment of any long-term effects of RZV in patients with IBD. Third, the sample size of this study was restricted by limited availability of RZV. Due to a national shortage of the vaccine at the time of initiation of the study, the majority of patients at our institution who have been prescribed RZV have not yet received the vaccine and were therefore not eligible for enrollment. Given that RZV was only recently approved for clinical use, our study serves as a pilot experiment, and our data may be useful in guiding future, larger studies with longer follow-up evaluating the safety of RZV in patients with IBD.

In conclusion, we observed a low rate of IBD flare after RZV administration (1.5%) in a cohort of patients with IBD in which two-thirds were immunosuppressed. Rates of local and systemic adverse reactions from RZV in this cohort were also similar to those seen in the general population. These findings may provide reassurance to providers and patients that RZV is safe in a real-world setting for patients with IBD. However, further comparative studies with larger number of patients and longer follow-up are needed to confirm that IBD and other immune-mediated diseases are not worsened after RZV administration.

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Author's contribution VRS, JR, and FAF helped in study concept and design; VRS and P-HL contributed to acquisition of data; VRS, P-HL, JR, TQ, AN, SKW, and FAF analyzed and interpreted the data; VRS, P-HL, JR, TQ, AN, SKW, and FAF drafted the manuscript; VRS, P-HL, JR, TQ, AN, SKW, and FAF critically revised the manuscript for important intellectual content; VRS helped in statistical analysis; and FAF supervised the study. Each author has approved the final draft of this manuscript

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Compliance with Ethical Standards

Conflict of interest Dr. Francis A. Farraye has served on advisory board for Glaxo Smith Kline. Venkata R. Satyam, Pei-Hsuan Li, Jason Reich, Taha Qazi, Ansu Noronha, Sharmeel K. Wasan declared that they have no conflict of interest.

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