Herpes Zoster Vaccine Response in Inflammatory Bowel Disease Patients on Low-dose Immunosuppression

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Background: Inflammatory Bowel Disease (IBD) patients are at an increased risk of developing herpes zoster (HZ), especially when immunosuppressed. HZ can be prevented with the herpes zoster vaccine (HZV), but many patients are not offered vaccination over concerns regarding efficacy and fear of adverse events. Although the Center for Disease Control and Prevention recommends that low-dose immunosuppression is not a contraindication, few IBD patients on these medications are receiving HZV.

Methods: This study was a prospective clinical trial to assess the safety and immunogenicity of HZV among 2 groups of IBD patients. Group A consisted of 14 patients on low-dose immunomodulators and group B consisted of 25 patients either on 5-aminosalicylic acid or no IBD therapy. Blood samples were obtained to measure immune responses.

Results: HZ specific immunoglobulin G rose significantly in both groups but the response was lower in the immunosuppressed group (P = 0.0002). Peripheral blood mononuclear cell secretion of Tumor necrosis factor-α in response to HZ antigen increased after HZV in group B, but not in group A. Interleukin-8 secretion increased in both groups, but the response was much higher in group B. There were no significant differences in adverse events between groups. No patients developed a HZ-like rash within 1 year after vaccination.

Conclusions: IBD patients on low-dose immunosuppressive therapy have a blunted immune response to HZV as compared with nonimmunosuppressed subjects. Despite this, immunosuppressed IBD patients are able to mount a statistically significant immune response. There were no serious adverse events to HZV.

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Key Words: immunization, Crohn’s disease, ulcerative colitis, vaccination

Current therapeutic options for patients with Crohn’s disease (CD) or ulcerative colitis (UC), including corticosteroids, immune modulators (such as 6-mercaptopurine [6-MP], azathioprine, methotrexate), and biologic agents (such as infliximab, adalimumab, certolizumab, golimumab, vedolizumab, and natalizumab), can cause systemic immunosuppression and increase the risk for developing infections such as pneumonia, influenza, disseminated varicella, and fulminant hepatitis. In contrast, the 5-aminosalicylic acid (5-ASA) compounds that are used to treat mild to moderate UC are thought to act topically and not cause systemic immunosuppression. Although several of these infections are potentially vaccine preventable, many patients with inflammatory bowel disease (IBD) on immune modulating agents are not being offered vaccination over concerns about the effectiveness and fear of adverse events.

Herpes zoster (HZ), commonly called shingles, is a localized, generally painful, cutaneous eruption that occurs most frequently among older adults and immunocompromised individuals. The disease results from the reactivation of latent varicella-zoster virus (VZV) within dorsal root ganglia. In the general population, about 1 in 3 persons will develop HZ or a HZ-related diagnosis, during their lifetime. This incidence increases with age due to weakening of cellular immunity. Many patients may also develop a debilitating postherpetic neuralgia.

Adults with IBD are also at an increased risk for developing HZ compared with the general population, independent of their pharmacologic therapy. The clinical course of acute HZ is variable; patients may present with a typical painful vesicular rash in a dermatomal distribution or with evident ophthalmic or systemic involvement. In a large retrospective cohort and nested case-control study, anti-TNFs, corticosteroids, and thiopurines were found to be independent risk factors for the development of VZV with highest risk associated with combination of immunosuppression or thiopurine immunomodulators.
In one retrospective study, the risk for developing HZ was greater in those patients with CD compared with UC and in those receiving immunomodulators and corticosteroids compared with those on 5-ASA. Although the majority of immunocompromised IBD patients only had cutaneous manifestations of HZ, many cases of systemic disease have been reported.

The herpes zoster vaccine (HZV), licensed in the United States (Zostavax) is a lyophilized preparation of a live attenuated strain of VZV (Oka/Merck). This vaccine uses the same strain as the varicella vaccines to prevent chicken pox, and was licensed and recommended in 2006 for prevention of HZ among adults aged 60 years and older. Its minimum potency is at least 14 times the potency of the single antigen varicella vaccine. Zostavax has been shown to be safe and efficacious in the prevention of HZ and generally well tolerated in clinical trials among subjects, 60 years old or older. In 2011, the Food and Drug Administration approved the use of Zostavax in adults aged 50 through 59 years based on a study of approximately 22,000 adults. Compared with placebo, Zostavax reduced the risk for developing HZ by 69.8% (95% CI, 54.1–80.6). However, the Advisory Committee on Immunization Practices declined to recommend the use of HZV among adults aged 50 through 59 years.

In 2008, the Advisory Committee on Immunization Practices, recommended that patients on “low doses of methotrexate (<0.4 mg·kg\(^{-1}\)·wk\(^{-1}\))”, azathioprine (<3.0 mg·kg\(^{-1}\)·d\(^{-1}\)), or 6-mercaptopurine (<1.5 mg·kg\(^{-1}\)·d\(^{-1}\)) for treatment of inflammatory bowel disease are not considered sufficiently immunosuppressed to create vaccine safety concerns and are not contraindications for administration of HZV. Despite these recommendations, very few IBD patients on these medications are receiving the HZV. In fact, work performed by our group has demonstrated that gastroenterologists’ knowledge regarding the appropriate vaccinations to be given to the IBD patient was generally poor. Although routine immunization of IBD patients with inactivated vaccines (such as influenza, pneumococcus) is an accepted (though not a commonly followed) practice, there remains considerable uncertainty and anxiety about the appropriateness of immunizing with the live vaccines. A case series of pediatric IBD patients on 6-MP or infliximab demonstrated that inadvertently administering the live, attenuated varicella vaccine did not result in varicella infection. Similarly, in a retrospective study of Medicare patients 60 years and older with immune disorders including IBD who were on biologic therapy, receipt of the more potent HZV was not associated with a short-term increase in HZ incidence, but was associated with a 39% lower incidence of HZ over a median of 2 years of follow-up. However, there is a paucity of data regarding the immune response to the HZV in IBD patients on immunomodulator therapy. Given the morbidity and mortality caused by the development of HZ in the IBD population, vaccinating patients against this virus may have important clinical implications.

Thus, the objective of this study was to characterize any adverse events associated with administration of HZV in IBD patients on thiopurines or methotrexate and to determine if IBD patients are able to mount an immune response to a single vaccination.

**METHODS**

**Study Population**

This study was approved by the Institutional Review Board at Boston University and was granted an exemption from the Investigational New Drug regulations from the Food and Drug Administration. IBD patients were recruited at the Center for Digestive Diseases at Boston Medical Center between November 2011 and July 2013. Inclusion criteria included patients who were of age 50 or older with a diagnosis of Crohn’s disease or ulcerative colitis confirmed by standard clinical, radiographic, endoscopic, and histopathologic criteria. Patients who had previously received HZV were excluded as were patients on anti-TNF agents. After informed consent, study patients were recruited and stratified into 2 groups: group A consisted of patients on low-dose immunomodulators and group B consisted of patients either on 5-ASA therapy or no IBD therapy. Group A, the low-dose immunomodulator group, included patients on methotrexate less than or equal to 0.4 mg·kg\(^{-1}\)·wk\(^{-1}\), azathioprine less than or equal to 3.0 mg·kg\(^{-1}\)·d\(^{-1}\), or 6-MP less than or equal to 1.5 mg·kg\(^{-1}\)·d\(^{-1}\). As part of the inclusion criteria, these patients had to be on a stable dose of low-dose immunomodulators for at least 3 months. There were no patients on corticosteroids at least 3 months before this study.

At the initial visit, patients had a comprehensive medical history and physical exam, completed the 10 question IBD questionnaire, provided a baseline blood sample, and then received the HZV (Zostavax; Merck, Whitehouse Station, NJ). Each patient was instructed to call the study team for the development of fevers, chills, rash, or any other concerning symptoms.

**Vaccination Follow-up**

Follow-up office visits were at weeks 2 and 6. At the week 2 visit the patients had a history and physical exam and provided a blood sample. In addition, patients received weekly follow-up phone calls at weeks 1, 3, 4, 5, and 52. During both the office and follow-up phone calls, patients were screened for adverse events, including fevers, chills, rashes, myalgias, arthralgias, headaches, injection site reactions, and visits to their primary care physician or an emergency department. None of the patients were lost to follow-up, however, on weeks 4 and 5, 1 patient was unable to be contacted to screen for adverse events.

**Evaluation of Cytokine Response**

Peripheral blood samples were obtained at baseline and 2 weeks postvaccination to measure immune responses to the vaccine. Peripheral blood mononuclear cells (PBMCs) were purified by Ficoll density gradient. PBMCs were cultured in the presence of 10 μg/mL of HZ virus antigen (Meridian Biosciences, Cincinnati, OH) or 1 μg/mL of anti-CD3/CD28 (eBioscience, $2.00$).
San Diego, CA) as a positive control for 3 days in Roswell Park Memorial Institute medium supplemented with 10% fetal bovine serum and 5 μM pen/strep (Sigma-Aldrich, Natick, MA). Cell-free supernatants were collected and evaluated for levels of secreted IFN-γ TNF-α, IL-10, and IL-8 by ELISA with reagents from R&D Systems.

**Measurement of Herpes Virus Specific Immunoglobulin G**

Plasma samples were evaluated for HZ-specific antibody levels at baseline and postvaccination by ELISA. Plates were coated with 15 μg/mL of HZ antigen (Meridian Biosciences) in phosphate buffered saline. After blocking with 1% bovine serum albumin/phosphate buffered saline, 5 serum samples were serially diluted from 1:20 to 1:2560 to define a dilution factor to allow measurement of immunoglobulin G (IgG) in all serum samples on 1 ELISA plate from each time point. The dilution factor of 1:320 was chosen based on a percent coefficient of variation and SD of greater than 50% on row means at each dilution (Fig. 2A). Antigen-specific IgG was detected with goat anti-human IgG (1:10,000; Southern Biotech, Birmingham, AL).

**Statistics**

Descriptive statistics, including proportions for categorical responses and mean (SD) for continuous responses were used to describe the sample. Chi-square and ANOVA techniques were used to compare outcomes between groups, as appropriate. The incidence of safety outcomes were compared between groups using chi-square or Fisher’s exact test. Paired t tests were performed to compare antibody responses to vaccination in both groups. A nonparametric Kruskal-Wallis test and posttest comparison specific groupings were performed to compare the IL-8 and TNF responses of both groups. Group sample sizes differ among the test because some patient samples were unavailable.

**RESULTS**

**Demographics**

A total of 39 subjects were enrolled in the study; two-thirds of patients had CD and one-third had UC. Group A included 14 patients on immunosuppressive therapy (azathioprine [n = 5], 6-MP [n = 6], and methotrexate [n = 3]). Group B consisted of 25 patients on 5-ASA therapy. Demographical and clinical characteristics of patients are summarized in Table 1. Ages were similar in both groups. There were no significant differences between groups by type of inflammatory bowel disease.

**Cellular Immune Response**

PBMCs from group A and B secreted similar levels of all cytokines measured under the control conditions, media only and the positive control anti-CD3/CD28 (Fig. 1A; shown is TNF-α secretion). In contrast, PBMCs from patients in group B increased TNF-α secretion in response to HZ viral antigens compared with PBMCs from group A (Fig. 1B). Similarly, IL-8, an indicator of acute inflammatory response, was elevated in response to HZ viral antigens by PBMCs from patients in group B (Fig. 1C); (P < 0.0001). Although IFN-γ and IL-10 were induced by PBMCs with anti-CD3/CD28 treatment, these cytokines were mostly low to undetectable in the majority of samples stimulated with the HZ virus antigens (not shown). Overall, these results suggest that patients in group A had reduced immune responses to the vaccine.

**Antibody Response**

We measured the effect of vaccination on serum levels of HZ-specific IgG. Mean and median baseline levels of HZ specific antibody were similar between group A and group B (data not shown). Similarly, there was no difference in the mean or median levels of HZ-specific IgG at 2 weeks postvaccination between group A and group B (Fig. 2B). However, we found a significant difference between the baseline level and 2 weeks postvaccination levels of antigen-specific IgG in individuals in both groups with group B demonstrating individual responses much stronger after vaccination compared with those in group A (Fig. 2B, C). The levels of antigen-specific IgG remained similar to levels measured at 2 weeks postvaccination in both groups (Fig. 2C).

**Adverse Events**

Though closely monitored, there was no significant difference in adverse events between groups throughout the 52 weeks follow-up period (see Table, Supplemental Digital Content, http://links.lww.com/IBD/B223). No participants developed a HZ like rash. In addition, none of the patients noted any change in their IBD quality of life as measured by the 10 question IBDQ during the 6 weeks intensive follow-up period. During this time period, none of the patients required a change in their IBD medications.

| TABLE 1. Demographics |
|---------------------------------|-------------------|-------------------|---|
| Characteristic | Immunosuppressed | No Immunosuppression | P |
| Total | 14 | 25 | 0.593 |
| Age (mean ± SD) | 60.4 ± 7.7 | 59 ± 6.9 | 0.344 |
| Sex (female) | 3 (21.4%) | 9 (36%) | 0.733 |
| IBD type | | | |
| Crohn’s disease | 10 (71.4%) | 16 (64%) | 0.733 |
| Ulcerative colitis | 4 (28.6%) | 9 (36%) | 0.733 |
| History of zoster | | | |
| Yes | 2 (14.3%) | 3 (12%) | 0.999 |
| Current medications | | | |
| 5-ASA | 2 (14.3%) | 24 (96%) | <0.001 |
| 6-MP | 6 (42.9%) | 0 (0%) | 0.002 |
| Azathioprine | 5 (35.7%) | 0 (0%) | 0.003 |
| Methotrexate | 3 (21.4%) | 0 (0%) | 0.040 |

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DISCUSSION

Our study demonstrates that IBD patients on low-dose immunosuppressive therapy with either a thiopurine or methotrexate have a blunted immune response to the HZV as compared with nonimmunosuppressed subjects. 6 MP, azathioprine, and methotrexate exert their anti-inflammatory functions by inhibiting RNA and DNA synthesis and thus cellular division. Patients on these medications have a reduced immune response to vaccines due to the inhibition of lymphocyte division and proliferation in follicles. In contrast, the mechanism of action of 5-ASA is more generalized resulting in the reduction of several inflammatory mediators. Our findings of a reduced immune response in patients with IBD on immunomodulators are similar to previously published data with inactivated vaccines.\textsuperscript{14,15}

Melmed et al\textsuperscript{14} demonstrated a diminished response to the pneumococcal vaccine (PPSV23) in patients on combined anti-TNF\textsubscript{x} and immunomodulator therapy. Another study evaluating the response to the influenza vaccine in IBD patients on either anti-TNF\textsubscript{x} monotherapy or combined therapy (anti-TNF\textsubscript{x} + immunomodulator) demonstrated a suboptimal response in the
combined therapy group compared with the monotherapy group.\textsuperscript{15} Similarly, in several studies of rheumatoid arthritis patients, a decreased response to vaccination was demonstrated among patients on thiopurines and methotrexate but not with anti-TNF therapy.\textsuperscript{16–19} Despite the blunted response, however, patients with IBD receiving immunosuppressive therapy were able to mount a statistically significant increase in acute cytokine responses (IL-8) and antigen-specific IgG after vaccination against HZ in our study. It remains unclear if this blunted response is clinically relevant and would afford protection, but our finding suggests that perhaps changing the vaccine dose may help overcome these deficiencies in immunosuppressed patients.

Because of the increased risk of developing HZ in IBD patients, many of whom are on immunosuppressive therapy, this study is particularly important. In this study, none of the patients developed HZ or varicella like rash at 1 year of follow-up after vaccination with HZV. In addition, there were no serious adverse events noted throughout the study. Minor adverse events, as noted on the package insert of the vaccine, including fever, rash, headache, arthralgias, myalgias, and injection site reactions were no different between the 2 groups of patients. Although we cannot draw any definitive conclusions about the safety of the live attenuated HZV in patients with IBD on low-dose immunosuppression given the small size of our study, our findings combined with the recommendations of the Center for Disease Control and Prevention, suggest that gastroenterologists can recommend administration of the HZV in this situation. Currently, HZV is contraindicated in patients on anti-TNF therapies. However, in a large retrospective cohort study of patients with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, and IBD, receipt of the HZV was not associated with a short term increase in incidence of HZ, including among those patients exposed to biologic agents. In fact, there was a decreased incidence (39%) of HZ over 2 years of follow-up.\textsuperscript{12} Given the increased risk of HZ in IBD patients on immunosuppression, recommendations from national societies are needed on the risks and benefits of administering the HZV in IBD patients on anti-TNF agents.

Several questions still remain unanswered. Important clinical questions regarding the optimal implementation of HZ vaccination programs to prevent HZ and its complications need to be addressed. Further research will be necessary to determine the clinical significance of the blunted immune response observed in our study and whether this response is protective or requires an altered vaccination protocol.

In addition, a better understanding of the epidemiology and risk factors for developing HZ could lead to changes in policy regarding the use of the HZV, such as targeting the vaccine to IBD patients younger than age 60 on immunosuppressive therapies. At the present time, although Food and Drug Administration approved for individuals of 50 and older, based on the Advisory Committee on Immunization Practice guidelines, the HZV is not licensed for persons aged <60 years. However, the increased burden of disease among younger IBD patients, including those of 50- to 59-year-old suggests that there may be a potential for expanding the indication of HZV to younger patients. However, because no long-term studies on the duration of vaccine protection have been performed for this age group, it remains unclear whether adults receiving the vaccine before age 60 will continue to be protected as they age. A clinical trial addressing the safety of HZV in rheumatoid arthritis patients on anti-TNF agents who are 50 years of age or older is underway (https://clinicaltrials.gov/ct2/show/NCT01967316).

In our study, we have demonstrated that although IBD patients on immunosuppressive therapy have a blunted response to the HZV, they did not develop any serious adverse effects at 1 year follow-up. We hope that our results alleviate concerns of practicing gastroenterologists and increase the use of HZV in the routine health maintenance of all their IBD patients, including those on low-dose immunomodulator therapy.

REFERENCES


