Review

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Vaccinations in Adult Patients with Inflammatory Bowel Diseases in the West

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Abstract
Background: Patients with moderate-severe inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis are commonly treated with long-term immunosuppressive therapies involving immunomodulators such as thiopurines, biologics (anti-TNF and anti-adhesion molecules), or novel small molecules such as Janus kinase inhibitors. ***Summary:*** Some infections seen with immunosuppressive therapy in IBD are preventable with vaccines. IBD-specific immunosuppressive therapy is generally initiated by gastroenterologists. Therefore, gastroenterologists should comprehend the appropriate application of vaccines such as hepatitis B, pneumonia, and herpes zoster vaccinations. This review summarizes the current guidance for vaccinations of IBD patients in the United States. ***Key Message:*** Gastroenterologists treating IBD patients must be aware of necessary vaccination schedules in the setting of immunosuppressive therapies.

Introduction

Inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, are immune-mediated diseases [1]. The immunosuppressive therapies used to treat the disease have been shown to increase the risk of infections in those with these conditions, including vaccine-preventable diseases [2–4]. In the United States, IBD typically affects younger adults who often do not have primary care providers. There are data indicating that patients with IBD do not receive preventive care at the same rate as the general population [5]. Other data reveal that IBD patients are specifically at risk for vaccine-preventable diseases as vaccination rates are low [3].

Reasons for low rates of vaccinations in IBD patients is the patients' lack of awareness and fear of side effects. However, gastroenterologists are also responsible, as they do not often take an immunization history or discuss immunizations with their patients [6]. A survey of American gastroenterologists revealed poor knowledge about recommended vaccinations for IBD patients [7]. Most gastroenterologists believed that the primary care provider was responsible for determining which vaccinations to give and

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for administering the vaccine. However, a survey of family physicians revealed that only 29% were comfortable making vaccine recommendations for their IBD patients [8].

A gastroenterologist may be the only medical provider a young IBD patient encounters. Therefore, it is imperative for gastroenterologists to understand immunization guidelines for IBD patients and convey these recommendations to a patient. To aid in this effort, the American College of Gastroenterology (ACG) updated guidelines in 2017 for preventive care in IBD patients [9]. A similar effort is made in Europe by the European Crohn's and Colitis Organization (ECCO), who recently published the "Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease" [10]. The overarching theme of these recommendations is that adults with IBD should receive age-appropriate vaccinations before initiation of immunosuppression when possible. Additionally, some attenuated live vaccination may be given in patients with low-dose but not with high-dose immunosuppression. In this review, we will summarize the literature and guidelines regarding pertinent vaccinations for adults with IBD in the Unites States.

Live Vaccines

Measles, Mumps, Rubella (MMR)

The United States has had a robust two-dose measles vaccination program since 1963 [11]. However, there has been a recent resurgence in measles outbreaks across the United States largely due to voluntary non-vaccination among some groups [12]. Furthermore, immunity may wane over time. One small single-center study demonstrated that a significant number of IBD patients lack immunity to measles [13]. The ACG guidelines recommend assessing measles vaccination history in all patients with IBD who are about to start immunosuppressive therapy. The MMR vaccine is a live-attenuated vaccine that is absolutely contraindicated in the setting of active immunosuppression. If vaccination history is unknown or there is no documentation of immunization in an IBD patient about to start immunosuppression, there is a conditional recommendation that the patient receive 2 doses of the MMR vaccine 28 days apart at least 6 weeks prior to the initiation of the immunosuppressive therapy [9]. In the Western world, where the overall prevalence of measles is low, the benefits of measles vaccination must be weighed against the risks of delaying the initiation of immunosuppressive therapy for 10 weeks.

Inactivated Vaccines

The general, conditional, recommendation from the ACG is that TDaP (tetanus, diphtheria, and acellular pertussis), HAV (hepatitis A), HBV (hepatitis B), and HPV (human papilloma virus) should be administered to all IBD patients per the guidelines set forth by the Advisory Committee on Immunization Practices (ACIP) [9]. There are select special considerations in IBD patients, however, specifically for the HBV vaccine.

Hepatitis B

In the United States, hepatitis B vaccination is only recommended with a specific risk factor. The need for immunosuppression is a risk factor [14]. Hepatitis B infection and reactivation are of great concern, especially if tumor necrosis factor-alpha (TNF-alpha) therapy is required, as fulminant and fatal cases of hepatitis B have been reported [15]. Despite this information and specific recommendations in guidelines, hepatitis B immunity rates among IBD patients are generally low and not often assessed by gastroenterologists [16]. IBD patients, especially those being treated with TNF-alpha agents, do not achieve hepatitis B surface antibody (HBsAb) levels that are adequate for immunity at the same rate of that of the general population [3, 17]. Therefore, the recommendation is to recheck titers 1 month after the last dose of a 3-dose regimen (0, 1, and 6 months). If there is no response to this initial course, then the recommendation is to re-vaccinate with the regular vaccine, revaccinate with a double-dose vaccine, or revaccinate with a combined HAV/HBV vaccine [9]. One small Spanish study demonstrates that the double-dose vaccination strategy is more effective than a standard-dose vaccination protocol [18]. There is no consensus, however, on the most appropriate method of revaccinating an IBD patient who is not responsive to the initial course of vaccination. The most important aspect is to assess hepatitis B exposure and vaccination status prior to initial of any immunosuppressive medicine in IBD. In fact, this is 1 of the 7 quality measures outlined by the American Gastroenterological Association (AGA) that is linked to reimbursement in the care of IBD patients [19].

Influenza

Patients with IBD are at an increased risk for influenza compared to age-matched non-IBD controls. This risk is heightened for those on immunosuppression [20, 21]. IBD patients who are infected with influenza have a higher likelihood of a serious outcome such as hospitalization

Table 1. Levels of immunosuppression according to the practice guideline for vaccination of the Infectious Diseases Society of America [37]

"Low-dose immunosuppression"
Prednisone equivalent <20 mg/day for <14 days
Methotrexate, 0.4 mg/kg/week
6-mercaptopurine, 1.5 mg/kg/day
Azathioprine 3 mg/kg/day
"High-dose immunosuppression"
Prednisone equivalent >20 mg/day for >14 days
Primary immunodeficiency disorder
Cancer chemotherapy
Within 2 months of solid organ transplant
HIV infection with CD4 count of 200/mm^3
Anti-TNF or rituximab use

or pneumonia [22]. For these reasons, annual inactivated influenza vaccination for all IBD patients on immunosuppression and household contacts of these patients is conditionally recommended by the ACG guidelines, as well as numerous other societies, including the European Crohn's and Colitis Organization (ECCO) [9, 10]. Despite this recommendation, rates of influenza vaccination in IBD patients are suboptimal [3, 6]. In a single-center study, less than a quarter of all IBD patients were vaccinated against seasonal influenza [23]. In this study, they found that immunosuppression was associated with a decreased likelihood of immunization against seasonal influenza. Those who visited a primary care provider at least once a year were more likely to be vaccinated against influenza. Patient education is also quite important as one study noted that provider recommendation was the third leading motivation for receiving the influenza vaccine [24].

Pneumococcal Diseases

Patients with IBD have a one and a half times higher rate of pneumonia compared to age-matched controls without IBD [25]. A large recent study demonstrated that IBD patients had an increased risk of invasive pneumococcal pneumonia both before and after the diagnosis of IBD. In this study, the risk of pneumonia was high even in patients with limited IBD medications, suggesting that the risk is related to the underlying alternation in the immune response and not immunosuppressive therapy itself [26]. Furthermore, IBD patients who are hospitalized for pneumonia are at an increased risk for death during the hospitalization [27].

Based on these data, the ACG issued a conditional recommendation that IBD patients receiving immunosuppression should receive pneumococcal vaccination with both the pneumococcal conjugate vaccine (PCV)-13 and the pneumococcal polysaccharide vaccine (PPSV)-23 [9]. The schedule is similar to that of national guidelines for those with chronic diseases: PCV-13, then PPSV-23 1 year later, and PPSV-23 5 years later [28]. However, rates of vaccination for pneumococcal diseases among IBD patients with immunosuppression are even lower than those of influenza vaccination. In one single-center study, only 9% of the IBD patients on immunosuppression received the pneumococcal vaccine [3]. As for other vaccines, common reasons for low rates of vaccination was the lack of patient awareness and the fear of side effects.

Herpes Zoster

Patients with IBD are at an increased risk for developing herpes zoster infections [29]. Treatment with corticosteroids and thiopurines are associated with higher odds of developing zoster [30]. The risk of zoster is highest, however, with a combination therapy of anti-TNF agents and thiopurine therapy [31]. In addition, the new Janus kinase inhibitor tofacitinib, which in the US is approved for the treatment of rheumatoid arthritis and moderate-severe ulcerative colitis, has a significant risk for zoster infections [32, 33]. As herpes zoster is a reactivation of the latent varicella zoster virus, it is typically associated with older age in the general population; however, in IBD patients, zoster can occur at a younger age [30].

Administration of the live-attenuated zoster vaccine (Zostavax®) was recommended for those over the age of 50 years [28]. The 2017 ACG guidelines issue a strong recommendation that even those IBD patients on "low-dose immunosuppression" (Table 1) should receive Zostavax [9]. More recent data suggest that Zostavax may be relatively safe in IBD patients on anti-TNF agents as well [34]. An older survey demonstrated that a third of the IBD patients over the age of 60 years recalled receiving the Zostavax [24].

A new inactivated formulation of the vaccine is available on the market in the US (Shingrix®) since the early 2018. This vaccine is recommended to be administered in 2 doses: the first dose at baseline and a second dose 2–6 months later [35]. Shingrix is also recommended for people who have already gotten the live shingles vaccine (Zostavax). However, currently, it is also only approved for healthy adults 50 years and older, thus insurance coverage for patients under 50 years is uncertain. In contrast to Zostavax, Shingrix is not contraindicated in pregnant women and immunocompromised adults, though its safety and efficacy in these populations have not yet been established

[36]. As it is an inactivated vaccine, it is presumably safe even for those patients on higher doses of immunosuppression, such as anti-TNF agent and combination therapy with anti-TNF and an immunomodulator as well. It is quite possible that having an inactivated vaccine that can be used for all IBD patients and the increased use of tofacitinib with the known risk of herpes reactivation will increase the rates of vaccination against herpes zoster.

Conclusion

IBD patients in the western world often consider their gastroenterologist their primary care provider. The immune alternation that is present with IBD and the immune-mediated therapies used to treat IBD increase the risk of infections in this patient population. Therefore, gastroenterologists must be aware of the complications of the disease and therapies, including vaccine-preventable diseases. In this review, we highlight pertinent vaccinations to consider in adult IBD patients in the Western world. Administration of the vaccines may be shared with other providers on the patient's care team. However, it is imperative that gastroenterologists educate IBD patients and their other health care providers on the recommended vaccinations.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

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