Efficacy of the vaccination in inflammatory bowel disease

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Received: May 29, 2012 Revised: August 21, 2012
Accepted: August 25, 2012
Published online: March 7, 2013

Abstract

Inflammatory bowel disease (IBD) is associated with conditions that may predispose to infections, such as the lack of an appropriate innate immune response to infectious agents, malnutrition, surgery, and immunosuppressive and biological drugs. Some of these infections may be preventable by vaccination. Therefore, for this particular patient population, the benefits of implementing a well-established immunization protocol in daily clinical practice are potentially even greater than for the general population. In recent years international consensus guidelines have been published, but in spite of these recommendations, studies have shown that a significant number of patients with IBD remain inadequately immunized. Another important issue regarding immunization in this population is that vaccine efficacy among patients receiving immunosuppressive therapies has been variable. In a healthy population, a humoral immune response to hepatitis B vaccination (HBV) is expected in > 90%, whereas a much lower rate is achieved in the IBD patients. Immunosuppressive, anti-tumor necrosis factor therapy and disease activity have been implicated in the impaired efficacy of the vaccination. The serological response to HBV should be confirmed and patients with an inadequate response should receive a second full series of vaccine. Modified dosing regimens, including doubling the standard antigen dose, might increase the effectiveness. Response to influenza, pneumococcal and tetanus immunization is still not clear, as there are studies that show a normal response to the vaccination while others demonstrate a lack of efficacy. We pose a series of questions on the efficacy of the different vaccinations recommended for IBD patients and attempt to answer them using scientific evidence.

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Key words: Vaccination; Efficacy; Infections; Immunization; Inflammatory bowel disease; Immunosuppressive medications; Hepatitis B vaccines; Influenza vaccines; Pneumococcal vaccines; Tetanus vaccines

Carrera E, Manzano R, Garrido E. Efficacy of the vaccination in inflammatory bowel disease. World J Gastroenterol 2013; 19(9): 1349-1353 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i9/1349.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i9.1349

INTRODUCTION

Current therapy for inflammatory bowel disease (IBD) patients often involves agents that suppress the immune system, placing them at an increased risk for developing infections. In recent years the scientific community has made an effort toward promoting preventative and prophylactic strategies against some of these infections. Several guidelines have been published specifically for the vaccination and immunization of patients with IBD. Although a consensus exists on the need to vaccinate these patients, it seems to be underused in clinical practice, and the response to immunizations in this group of patients and the factors influencing this efficacy is unknown.
ARE IBD PATIENTS CORRECTLY VACCINATED IN CLINICAL PRACTICE?

When we try to elucidate the real efficacy of vaccinations in IBD patients, the first question we have to answer is if physicians are following the immunization and vaccination recommendations provided by the guidelines. Several studies have reported on apparent knowledge deficiencies among gastroenterologists, and show that a significant number of patients remain inadequately immunized. Yeung et al. assessed 167 patients and 43 gastroenterologists for immunization attitudes, knowledge and practice. Only 14% of the gastroenterologists surveyed reported taking an immunization history from most of their patients, and the majority of patients felt they did not have enough information about immunizations. Similar data were highlighted in another study, where around a half of the gastroenterologists surveyed remembered asking their patients about their immunization history. Melmed et al. assessed risk of exposure and immunization status among patients receiving care in an IBD specialty clinic. While about 44% of patients had at least one risk factor for hepatitis B, only 28% had been vaccinated against the infection. Only 45% of the patients in this study recalled receiving a tetanus immunization within the past 10 years, 28% reported regular flu shots and 9% reported having received the pneumococcal vaccine. A Spanish multicenter study detected vaccination against hepatitis B in only 12% of IBD patients.

About 20% of the gastroenterologists surveyed reported that they did not know how important it was for their IBD patients to be up to date on specific immunizations before starting immunomodulating or biological therapy. In summary, the lack of awareness of vaccination recommendations puts IBD patients at risk of infections which might easily be avoided through a more intensive vaccination program.

HOW EFFECTIVE ARE VACCINATIONS IN IBD PATIENTS?

Vaccine efficacy is defined as percent risk reduction for clinically significant infection in a vaccinated group versus a control group. Vaccination is a proven and well-established strategy for preventing infectious diseases in the general population. However, immunosuppressive illnesses in general are associated with reduced immunogenicity following vaccination. Moreover, patients receiving immunosuppressive therapy may have a suboptimal serological response after a variety of vaccinations.

Hepatitis B virus

A standard 3-dose hepatitis B virus (HBV) vaccination induces protective antibody concentrations in approximately 95% of healthy individuals. However the response rate to HBV is lower in patients with IBD, especially in those receiving immunosuppressive or biological therapies. In a study published by Vida et al., where 43% were on immunosuppressive therapy, only 36% of patients achieved adequate hepatitis B surface antibody (HBsAb) levels (defined as > 10 IU/L). Melmed et al. report similar data in a study where only 33% of the subgroup of patients who were immunized had detectable antibodies to hepatitis B surface antigen (anti-HBs) titers. According to the World Health Organization, an HBsAb concentration ≥ 10 IU/L is considered a reliable marker of protection against infection.

As time passes, HBsAb titers frequently diminish and become undetectable. Among immunocompromised patients who respond to the vaccine, clinical HBV infection has been documented in those who do not maintain a HBsAb concentration of ≥ 10 IU/L. Based on this evidence, in the United Kingdom seroprotection against hepatitis B was redefined at ≥ 100 IU/mL, especially in those with chronic diseases or with immunosuppressive therapies. A recent study published by Altunöz et al. defined the effective immune response as an antibody level > 100 IU/L after comparing the efficacy of the standard 3-dose vaccine in a group of IBD patients and comparing it to a control group. The effective immune response was significantly higher in the control group compared to the IBD group (89% vs 53%).

The response rate to the HBV vaccine seems to be quite low in IBD patients. Modified dosing regimens, including doubling the standard antigen dose, might increase response rates in immunocompromised patients. Chaparro et al. assessed the efficacy of the HBV vaccine at a double dosage (0, 1 and 2 mo) in IBD patients and found that 60% of the IBD patients had adequate HBsAb titers (≥ 10 IU/mL), but only 34% achieved adequate immunity (≥ 100 IU/mL).

Influenza

Since influenza infection may result in serious illness in immunocompromised individuals, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommends influenza vaccination for all immunosuppressed patients. Several studies have concluded that the influenza vaccine is safe and effective in both children and adults with various chronic diseases. However, the immune response in immunocompromised patients varies. Most studies attempting to identify the efficacy of the influenza vaccine in IBD patients have been carried out in the pediatric population. Manula et al. compared response to influenza vaccine in children with IBD and observed that the IBD group mounted less effective responses to one-third of antigens compared to controls, while patients on a combination of biologics and immunomodulators had an impaired response to two-thirds of antigens. In contrast, Lu et al. assessed the response rates to influenza vaccinations in IBD children and reported similar responses among IBD patients, regardless of their immunosuppressive status. A recent study performed in adults came to
similar conclusions and demonstrated that IBD patients on immunosuppressive treatment are able to mount an effective immune response\cite{40}.

**Pneumococcal**

Melmed \textit{et al} \cite{41} assessed response to pneumococcal vaccine in IBD adults compared to controls. Patients treated with a combination of biologics and immunosuppressants presented with an impaired response to the pneumococcal vaccine compared to controls and patients not receiving immunosuppressive therapy. Dotan \textit{et al} \cite{42} reported contradictory results in a recent study where they concluded that IBD patients do not have an intrinsic immunodeficiency and display a significant increase in titers for all pneumococcal serotypes.

**Tetanus**

Response to tetanus immunization in IBD patients is not clear, as there are studies\cite{44,46} that demonstrate that IBD patients have a normal response to the tetanus vaccine, while others\cite{47} suggest an impaired anti-tetanus response.

**WHAT ARE THE FACTORS THAT AFFECT THE EFFICACY OF VACCINATION IN IBD PATIENTS?**

In healthy individuals, several risk factors for non-response to hepatitis B vaccination have been described, such as smoking, older age, male gender and a high body mass index\cite{45}. Influenza immunization may be less effective for those in the general population with certain medical conditions, such as systemic lupus erythematosus\cite{48} or patients receiving immunosuppressive treatments\cite{49}.

The lack of response to vaccines by IBD patients may be due to associated immunosuppressive and anti-tumor necrosis factor (TNF) treatments rather than IBD per se. In this sense, some authors have demonstrated a suboptimal response to pneumococcal vaccination in patients with IBD under combination therapy with anti-TNF drugs and immunosuppressants\cite{50}, while IBD patients who received non-immunosuppressive therapy exhibited a good response to the vaccine\cite{51}.

Patients on anti-TNF agents have demonstrated a decreased immune response to influenza vaccine in IBD and non-IBD populations\cite{22,24,28,50}. HBV vaccination is also influenced by the medication administered. In a study by Chaparro \textit{et al} \cite{50}, 40% of patients had an adequate response to immunization (> 100 IU/L), while the response was much lower in patients undergoing biological therapy (10%), although this difference did not achieve statistical significance, probably due to the small size sample. Altunöz \textit{et al} \cite{52} assessed immune response to HBV vaccination, and demonstrated in their subgroup analysis that the group of patients not under immunosuppressive treatment achieved an adequate immune response (> 10 IU/L) in 91% and an effective immune response (> 100 IU/L) in 73%, whereas only 61% and 29% of patients under immunosuppressive therapy, respectively, acquired an adequate and effective immune response. There are contradictory results by Vida \textit{et al}\cite{53} that could not demonstrate the effect of immunomodulators on the efficacy of the HBV vaccine. The small sample size and corresponding low statistical power may explain the lack of statistically significant differences. In fact, a tendency towards a lower rate of response to vaccine was found in the immunosuppressed group\cite{54}.

Disease activity has also been implicated in impaired responses to vaccination. In this respect, a subanalysis in the study by Altunöz \textit{et al} \cite{50} concluded that active IBD patients achieved a significantly lower response to vaccination compared to patients in remission (41% vs 63%). Thus, these authors recommend HBV vaccination during remission periods.

In summary, patients receiving anti-TNF therapy, immunosuppressants, or with active disease, are at risk of developing an inadequate serologic response. Future studies should attempt to determine if booster immunizations are needed in this group of patients\cite{55}. Further studies should determine if other factors such as genetics, gender or age could affect the response to immunization in IBD patients.

**WHAT CAN WE DO IF REGULAR VACCINATION IS NOT EFFECTIVE?**

Although routine serology testing for immunity is not recommended after HBV vaccination in adults, post-vaccination serology is advisable for high-risk individuals such as the immunocompromised, including IBD patients\cite{16,24,28,50}. Recommended seroprotection against HBV in immunosuppressed patients is defined as HBsAb ≥ 100 IU/mL\cite{56}. In HBV immunization studies, 25%-50% of the patients that do not respond to a primary three-dose vaccine responded to an additional dose, and 44%-100% respond to a second three-dose course. Therefore, those patients that do not achieve an adequate immune response after the primary immunization should be revaccinated with three additional doses\cite{51}. Moreover, revaccination with a three-dose regimen using a double dose has also been suggested\cite{52}. Mamula \textit{et al} \cite{57} propose a second booster dose of influenza vaccine in IBD patients with concomitant immunomodulatory and anti-TNF treatment. There are no other recommendations for the remaining vaccinations.

In conclusion, IBD patients are considered to be at risk for several infections and should therefore be immunized. Response to immunization in this group of patients is still a controversial issue. Further studies are necessary in order to clarify the true efficacy of these vaccinations and to provide recommendations on specific situations such as failure to respond. In spite of the aforementioned recommendations, several studies demonstrate that vaccines are under-prescribed and that intensive educational efforts are required in order to ensure correct adherence to the set guidelines by gastroenterolo-
gists and primary care physicians.

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