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Review Article

Immunisation in children and adolescents with inflammatory bowel disease

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ABSTRACT

Inflammatory bowel disease (IBD) patients may be at a higher risk for developing infections due to underlying disease, malnutrition, surgery, or immunosuppressive therapy. Therefore, protecting this group against infections is of particular importance. Immunisation against vaccine-preventable diseases is strongly recommended. This article for the first time summarises data on immunogenicity and safety of vaccines in IBD children and provides an update on some important issues regarding immunisation in these group of children.

Contents

1. Introduction

Inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD), are multifactorial polygenetic diseases with heterogeneous genetic causes [1]. The long-term treatment for IBD involves the use of anti-inflammatory agents and immunosuppressive medications including steroids, anti-metabolites and biologic therapies [2]. IBD patients are considered immunocompromised as a result of these treatments [3]. IBDs are usually more complicated in children than in adults [4]. Therefore, the majority of children with IBD are aggressively treated using a combination of immunosuppressive and biologic drugs.

Bacterial and viral vaccine-preventable infections occur in individuals in all age groups. However, many of these infections predominantly occur in the paediatric population. As with other infections, vaccine-preventable infections are more frequent in immunosuppressed subjects and may have a more severe disease course in these subjects [5,6]. Thus, children with IBDs have a greater risk of suffering from vaccine-preventable diseases due to their immature immunologic system and the immunosuppressive treatments for IBDs. Similar to other children and adolescents, patients with IBDs spend time in school and day-care centres and may contract microbes. Although the hypothesis that IBDs are a result of an impaired or altered immune response to environmental and infectious factors is not fully supported, many different infections could result in an IBD flare [7]. Moreover, infections may

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worsen the clinical status of IBD patients. Hepatitis A virus infection has a particularly high mortality rate in patients with chronic liver disease and the 5–10% of IBD patients who have clinically significant hepatobiliary manifestations [8–11]. Additionally, in patients with chronic hepatitis B, the immunosuppression induced by IBD treatment could facilitate viral replication, leading to a flare or to the exacerbation of hepatitis [12].

Due to underlying disease, malnutrition, surgery, or immunosuppressive therapy, IBD patients may be at a higher risk for developing infections [13]. Therefore, protecting this group against infections is important. A committee formed by the Crohn's and Colitis Foundation of America (CCFA) [14] and by the European Crohn's and Colitis Organisation (ECCO) stated that IBD patients would benefit from immunisation against vaccine-preventable diseases [15]. However, these statements are not directly focused on the paediatric age group. The aim of this article is to present the important issues regarding immunisation in paediatric patients with IBD.

2. Review

2.1. Immunisation schedule in children with IBD

According to the CCFA [14] and the ECCO [15], children with IBD should follow the routine childhood immunisation schedule (available on the website of American Academy of Pediatrics (AAP)) [16] with one exception. The exception is that the use of live vaccines in immunosuppressed patients is generally contraindicated. It is strongly recommended that an immunisation history is obtained at the time of IBD diagnosis. It is critical that the administration of live vaccines, such as the varicella vaccine, occurs before treatment with immunosuppressive or biological medications is initiated.

There is no clear definition of an immunocompromised state. Given that no evidence exists of a systemic immune defect in patients with IBD, these patients can become immunocompromised only as the result of their treatment. Based on an expert consensus report [14,17], immunosuppression in IBD patients is defined as the following:

- The period of treatment with glucocorticoids (GKS) (prednisone dose of 20 mg/day or equivalent or 2 mg/kg/day for children weighing less than 10 kg, for 2 weeks or more) and the 3 months following therapy cessation. However, several authors suggest that the post-therapy period may be curtailed to 4 weeks [17];
- The period of treatment with effective doses of 6-mercaptopurine/azathioprine, methotrexate or other biologics and the 3 months following therapy cessation; or
- Periods of significant malnutrition.

Although no data exist regarding the appropriate interval between live-virus vaccination and the introduction of immunosuppressive therapy, waiting for $\geq$4 weeks after varicella vaccination and $\geq$6 weeks after MMR vaccination is recommended [17,18].

2.2. Vaccine immunogenicity in children with IBD

The immunosuppressive effects of IBD treatment could compromise the natural immune response following immunisation and could impact the efficacy and safety of vaccination [19,20]. The ECCO has emphasised the need for further research to evaluate the immune response to various types of vaccines in IBD patients [15]. There are currently a limited number of studies that have assessed post-vaccination immunity in paediatric IBD patients. These studies are summarised in the next sections.

The inactivated influenza vaccine is the best-studied vaccine in paediatric IBD patients. Prospective studies have evaluated 278 patients in influenza seasons during the years 2002 and 2012 in different countries [21–24]. The results of these four studies were consistent and demonstrated that the inactivated influenza vaccine is generally immunogenic and safe in this patient population. Although children with IBD achieved appropriate immunity to influenza A, their immunity to influenza B appeared to be diminished in the patients undergoing immunosuppressive therapy. In all studies, children with IBD had a lower rate of seroconversion than healthy controls against one of the three influenza strains in the vaccine.

In two studies assessing the immune response to the hepatitis A vaccine, 97–100% of children with IBD achieved seroprotection [25,26]. There was no significant difference in the rate of seroconversion between IBD patients and healthy controls.

There are also two studies that evaluated immune responses in children with IBD after receiving the hepatitis B vaccine. Moses et al. found that 51% of previously vaccinated children with IBD did not have protective anti-HBs levels, i.e., anti-HBs level $\geq$10 mIU/ml [27]. Moreover, 34 of the patients received a booster immunisation, and 8/34 (24%) did not have an anamnestic response. In a study by Urganci et al. [25], 70% of IBD patients achieved seroprotection (defined as above) 1 month after primary hepatitis B vaccination compared to 90% of healthy controls. This difference was statistically significant. In the individuals that did not achieve seroprotection after the single booster, the proper anti-HBs level was found in 50% of IBD patients and 60% of controls. The overall seroprotection rates were 85% in IBD patients and 96% in controls after the entire (primary and booster) hepatitis B vaccine series; the difference was not statistically significant. Additionally, there was no significant reduction observed in the antibody responses of IBD patients and controls during the follow-up period.

In two studies conducted examining children with IBD who were treated with infliximab, the response to primary vaccination was considered satisfactory when assessed shortly after vaccination but decreased thereafter [27,28]. The anamnestic response rate after the vaccine boost was as high as 76% [27]. It is known that the anti-HBs levels decrease over time in some subjects who respond well to vaccination against hepatitis B. However, memory B cells have the capacity to respond rapidly via clonal expansion and differentiation of plasma cells secreting high-affinity antibodies. Thus, additional doses of the vaccine can be used to boost the immune response. In a study by Moses et al., 87% of children with IBD who were treated with infliximab seroconverted following hepatitis B vaccination [27].

There is a paucity of data regarding immune responses to live vaccines in children with IBD because these vaccines are not recommended in immunosuppressed children with IBD. A study examining a series of 6 children and adolescents who were vaccinated against varicella indicated that all but 1 patient developed immunity after vaccination [29]. This study is very important because it is the only report describing live-virus vaccination in IBD patients receiving immunosuppressive treatment (5/6 children were receiving 6-MP and 2/6 were receiving infliximab). Moreover, this study considered the varicella vaccine to be safe for immunosuppressed IBD patients. Although the results of the study are promising, the case series is small (6 people), and a majority of patients (5/6) had received one dose of the varicella vaccine before the initiation of immunosuppression. Therefore, more data are needed to change the recommendations regarding the use of attenuated vaccines in immunosuppressed IBD patients. Varicella zoster virus is of particular interest in IBD because there are many reports of severe, disseminated, and occasionally fatal varicella infections in immunosuppressed IBD patients [30].

In most of these studies, there is a significant reduction in the serological response to a vaccine observed in patients treated with immunomodulators and biological drugs. However, the rates of vaccine-elicited responses were satisfactory. The response rates varied in different studies and ranged from 100% [25] to 49% [27].