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Immunogenicity and mechanisms impairing the response to vaccines in inflammatory bowel disease

Alicia C Marín, Javier P Gisbert, María Chaparro

Alicia C Marín, Javier P Gisbert, María Chaparro, Gastroenterology Unit, Hospital Universitario de La Princesa and Instituto de Investigación Sanitaria Princesa, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, 28021 Madrid, Spain

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Correspondence to: María Chaparro, MD, PhD, Gastroenterology Unit, Hospital Universitario de La Princesa and Instituto de Investigación Sanitaria Princesa, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Americio 17 portal E 2 °C, 28021 Madrid, Spain. mariaachs2005@gmail.com
Telephone: +34-91-3093911
Fax: +34-91-4022299

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Abstract

Inflammatory bowel disease (IBD) is an immunological disorder that is usually treated with immunosuppressive therapy, potentially leading to increases in vulnerability to infections. Although many infections can be prevented by vaccination, vaccination coverage in these patients in clinical practice is insufficient. Therefore, the seroprotection condition should be verified, even for routine vaccines, such as hepatitis B or pneumococcus. Response to vaccines in IBD patients is thought to be impaired due to the immunological alterations generated by the disease and to the immunomodulatory treatments. The immunogenicity of hepatitis B, influenza, and pneumococcal vaccines is impaired in IBD patients, whereas the response to papillomavirus vaccine seems similar to that observed in the healthy population. On the other hand, data on the immunogenicity of tetanus vaccine in IBD patients are conflicting. Studies assessing the response to measles-mumps-rubella, varicella, and herpes zoster vaccines in IBD patients are scarce. The cellular and molecular mechanisms responsible for the impairment of the response to vaccination in IBD patients are poorly understood. Studies aiming to assess the response to vaccines in IBD patients and to identify the mechanisms involved in their immunogenicity are warranted. A better understanding of the immune response, specifically to vaccines, in patients with immune-mediated diseases (such as IBD), is crucial when developing vaccines that trigger more potent immunologic responses.

Key words: Crohn's disease; Inflammatory bowel disease; Tumor necrosis factor; Ulcerative colitis; Vaccine; Vaccination; Immunogenicity

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Core tip: Inflammatory bowel disease (IBD) patients

are vulnerable to infections owing to the underlying immunological disorder and to the immunosuppressive therapy used to treat the disease. Although some of these infections could be vaccine-preventable, IBD patients show impaired immunogenicity to some vaccines (such as hepatitis B or pneumococcal vaccines). In this review, the authors discuss available data on the immunogenicity of vaccines in IBD patients and summarize current knowledge on the mechanisms that could impair responses to vaccines.

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INTRODUCTION

Crohn's disease and ulcerative colitis are the two main inflammatory bowel diseases (IBD). Treatment during the last decade has been based on immunosuppressants and biological therapies, such as anti-tumor necrosis factor alpha (TNF) agents^[1]. Immunosuppressants and biologics are used increasingly often and earlier during the course of the disease^[1]. In this respect, patients with IBD are vulnerable to infections because of the immunological disorder caused by the disease itself or to the immunosuppression induced by the treatments.

Prevention of infectious diseases is a major issue for public health, and vaccination has shown to be one of the most successful strategies against the spread of several diseases. Accordingly, the European Crohn's and Colitis Organisation (ECCO) recommends knowing the seroprotection condition of IBD patients, even for routine vaccines, such as hepatitis B or pneumococcus^[2] (Tables 1 and 2). Although numerous groups and experts support the importance of adequate vaccination of IBD patients, the percentage of physicians that monitor and routinely recommend the administration of vaccines to IBD patients is low (approximately 50%)^[3-5].

Some studies have suggested that the response to vaccines in IBD patients is impaired^[6-10]. The disease-related immune disorder and the immunosuppression induced by the medications could compromise the natural response to immunization and impact the immunogenicity and safety of vaccination in this particular population.

The present review will focus on the immunogenicity of vaccines in patients suffering from IBD and the mechanisms that are potentially involved in impaired response to vaccines.

INACTIVATED VACCINES

Hepatitis B virus vaccination

The prevalence of hepatitis B virus (HBV) infection does not significantly differ between the background population and patients with IBD^[11]. However, reactivation of HBV may have fatal consequences in immunosuppressed patients. In this respect, the authors of the REPENTINA 2 study observed that among 25 patients with hepatitis B surface antigen (HBsAg), nine experienced liver dysfunction and six had liver failure^[12]. Thus, active preventive measures, such as administration of antiviral drugs, to patients with chronic infection and vaccination of seronegative patients are recommended^[2].

Recombinant HBV vaccines mainly consist of HBsAg associated with adjuvants that enhance the immune response (e.g., monophosphoryl lipid A, aluminium hydroxide, oil-in-water emulsions). Studies in healthy individuals showed that three doses of HBV vaccine were enough to develop protective anti-HBs antibody titers in over 95% of the population^[13-15]. However, the immunogenicity of this vaccine in IBD patients has proven to be lower, mainly in those patients receiving biologic therapy or immunosuppressants^[16,17]. For example, Melmed *et al.*^[18] detected anti-HBs antibodies in only three out of nine patients, and Vida Pérez *et al.*^[19] in 36% of the vaccinees. In another study with a single-dose vaccine at 0, 1, and 6 mo, an appropriate immune response (*i.e.*, > 10 IU/L) was obtained in all healthy controls, but only 76% of patients were able to reach that cutoff^[6].

The largest study to date on HBV vaccination in IBD patients was performed by Gisbert *et al.*^[20]. A total of 241 patients were vaccinated against HBV with a quick schedule (0, 1, and 2 mo) and a double-dose protocol. Fifty-nine percent and 39% of the patients developed, respectively, anti-HBs titers > 10 IU/L and > 100 IU/L two months after the last dose. In this study, older age and anti-TNF treatment were associated with a lower response rate.

These findings were confirmed by Loras *et al.*^[21], who studied 254 patients (235 with anti-HBs < 10 IU/L and 19 with anti-HBs from 10 to 100 IU/L). In this study, only 26% of patients achieved anti-HBs titers > 100 IU/L. Age ≤ 30 years and starting the vaccination schedule simultaneously with anti-TNF treatment (*vs* months to several years of anti-TNF treatment) were the only predictors of effective vaccination.

The second ECCO consensus on opportunistic infections suggested that the development of seroprotection might require higher doses of the VHB immunogen^[2]. The benefit for vaccinating with a high-dose protocol was demonstrated by Gisbert *et al.*^[22], who studied 148 patients vaccinated against HBV using two different protocols: 54% with the "clinical

Table 1 Vaccines recommended in patients with inflammatory bowel disease

Vaccine	Type of immunogen	General recommendations for vaccination in IBD	Concerns in IBD patients on immunosuppressive therapy
HBV	Recombinant protein	After checking the serological status for HBV: double-dose schedule	None
HPV ¹	Quadrivalent vaccine (Recombinant proteins)	Women aged between 11-12 yr: 3 doses (0, 2 and 6 mo)	None
Influenza	Inactivated virus	1 dose annually	None
Pneumococcus	Polysaccharides, conjugated or not to a protein carrier	1 dose every 5 yr	None
Tetanus	Inactivated toxoid	Patient previously vaccinated: 1 dose every 10 years Unknown or not previously vaccinated: 3-doses	None
Measles-mumps-rubella	Live attenuated virus	Non-immunized: Standard schedule	Contraindicated
Varicella	Live attenuated virus	Non-immunized: 2 doses (0 and 1-2 mo)	Risks and benefits should be evaluated on an individual basis
Herpes zoster ¹	Live attenuated virus	Patients aged over 60 yr: Standard schedule	Risks and benefits should be evaluated on an individual basis

¹Depending on local recommendations. Source: Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease^[2]. IBD: Inflammatory bowel disease; HBV: Hepatitis B virus; HPV: Human papillomavirus.

Table 2 Vaccines recommended in patients with inflammatory bowel disease and mechanisms associated with impaired response in these patients

Vaccine	Immunogen	Impaired response	Factors associated with a lower response	Mechanisms associated with lower immunogenicity
HBV	Recombinant protein	Yes	Age ^[20,21,23] , immunosuppressive or anti-TNF therapy ^[20,21,23]	Not described
HPV	Recombinant protein	No	-	-
Influenza	Inactivated virus	Yes	Immunosuppressive therapy ^[8]	Not described
Pneumococcus	Polysaccharides	Yes	Immunosuppressive and/or anti-TNF therapy ^[9,10,55]	Conflicting results about memory B cells ^[60,62]
Tetanus	Inactivated toxoid	Unclear	None described	Defects in the development of IgG-secreting plasma cells ^[65]
Measles-mump-rubella	Live attenuated virus	No	-	-
Varicella	Live attenuated virus	No	-	-
Herpes zoster	Live attenuated virus	No	-	-

HBV: Hepatitis B virus; HPV: Human papillomavirus; TNF: Tumor necrosis factor.

practice" protocol (single doses of Engerix-B[®] at 0, 1, and 6 mo) and 46% with a faster, double-dose protocol (double doses of Engerix-B[®] at 0, 1, and 2 mo). A higher effective response to vaccination (defined as anti-HBs > 10 IU/L) was reached with the faster double-dose schedule than the response obtained with the single-dose protocol (75% vs 41%). The double-dose protocol was the only factor associated with a better response to the vaccines, suggesting that the faster double-dose schedule could be a suitable option in patients with IBD^[22].

Although the double-dose regimen was more immunogenic than the standard dose, the response to HBV vaccine in IBD patients was still too low compared to healthy controls. Chaparro *et al.*^[23] assessed the immunogenicity of a recombinant vaccine with a new adjuvant, Fendrix[®], compared with double-dose Engerix[®] at 0, 1, 2, and 6 mo in IBD patients. A four-dose vaccine schedule significantly increased (by > 40%) the response compared with

the three-dose regimen. Older age and treatment with immunosuppressants or anti-TNF drugs impaired the success of the vaccines.

Therefore, despite the numerous attempts to enhance the response to HBV vaccines either by increasing the dosage, optimizing the administration schedule, or testing potent new adjuvants, the response rate to HBV vaccine in IBD patients was still impaired.

The success of the recombinant HBV vaccine depends mainly on the T-cell response to the antigen. However, before such a response can occur, antigen-presenting cells must be able to present the antigen to the T cells, and B cells must be able to proliferate and differentiate into anti-HBs-secreting plasma cells. Thus, the development of protection against HBV will largely depend on the ability of the immune system to produce anti-HBs antibodies. Nevertheless, long-term protection against infection may also require generation of immune memory cells (B and T memory

lymphocytes)^[24].

The response to HBV vaccine does not only depend on the type and dosage of HBV vaccine. Vaccinee characteristics, such as age, gender, the presence of certain genetic polymorphisms, comorbidity, immune status, or smoking habit, also affect the immunogenicity of the HBV vaccine^[25].

Many studies have investigated the immune mechanisms associated with the responsiveness to HBV vaccine in the healthy population. For example, an association between human leukocyte antigen (HLA) haplotypes and defects in the presentation of HBsAg (by antigen-presenting cells) and recognition HBsAg (by T lymphocytes, affecting their cytokine production profile) has been described^[26]. The role of lymphocytes in triggering the immune response has also been investigated, and defects in the lymphocyte repertoire or functionality have been documented^[27-29], as has the presence of T-cell populations that suppress the cellular response to HBsAg^[30] and abnormal regulatory T-cell counts^[31]. Finally, diminished activation of natural killer (NK) and natural killer T (NKT) cells has also been associated with a poorer response to this vaccine^[32].

Immune-mediated or chronic viral diseases, such as human immunodeficiency virus (HIV) infection and chronic liver or kidney disease, have also been associated with impaired responsiveness to the HBV vaccine. For example, it has been suggested that one of the main reasons for vaccine failure in patients with chronic viral infections [HIV, hepatitis C virus (HCV)] is the limited proliferative potential of the lymphocyte associated with changes (induced by the infective virus) in the signaling immune mechanisms^[33]. Furthermore, an impaired T-helper response has been reported in patients on dialysis^[34]. On the other hand, biological parameters, such as higher helper T-CD4 prevaccination counts in HIV-infected patients^[35] or a higher CD4/CD8 ratio in dialysis patients^[36], have been shown to predict a better response to vaccination.

In IBD patients, data on the cellular or molecular mechanisms impairing the immunogenicity of HBV vaccine are scarce. Several of the genetic mutations and polymorphisms associated with an increased risk of developing IBD have also been involved in recognition of intestinal microbiota by the innate immune system (*NOD2*, *TLR4*), in autophagy (*ATG16L1*, *IRGM*, *VAMP3*), in intestinal barrier function (*DLG5*, *MUC1*), and in the activation, survival, and growth of lymphocytes (*HLA*, *IL23R*, *IL10*, *IL10R*, *IL2RA*, *ERAP2*, *CPEB4*, *TNFSF11*, *SMAD3*)^[37,38]. The genetic and immunological peculiarities of patients with IBD described above, together with the effect of the immunomodulatory therapies, could, therefore, affect the ability of the immune system to react properly to the vaccine antigens.

Human papillomavirus vaccination

Human papillomavirus (HPV) infection is a sexually

transmitted disease that comprises some 40 oncogenic variants classed as low to high-risk to develop an anogenital neoplasm^[39-41]. As HPV-associated tumors may be more common after prolonged immunosuppressive therapy^[2], vaccination has been recommended in patients with HPV infection^[41].

Since 2006, a quadrivalent vaccine that covers types HPV-6, -11, -16, and -18, is accessible in Europe. In 2007, a bivalent vaccine for types HPV-16 and -18 was authorized. Both prophylactic vaccines are effective and safe against HPV in the immunocompetent population (95%-100%)^[42,43].

Jacobson *et al*^[44] assessed the immunogenicity and tolerability of the quadrivalent HPV vaccine in IBD patients receiving immunosuppressive therapies and in healthy controls. The study included 33 IBD patients who received three doses of Gardasil[®] at 0, 2, and 6 mo. After the three doses, 94% of the patients seroconverted to the four subtypes of HPV, and only 6% were not seropositive to type HPV-18. This figure was similar to that described in healthy individuals. Unfortunately, owing to the small sample size, the study did not provide data on differences in immunogenicity between the different drug doses (immunomodulators vs anti-TNF agents).

Influenza virus vaccination

Influenza is a seasonal respiratory disease that, despite its usual acute and self-limiting behaviour, leads to many thousands of visits to emergency departments and can be lethal^[8,45,46]. Rates of morbidity and complications have been reported to be higher among immunosuppressed patients^[47,48].

The A and B types of the virus are responsible for human influenza epidemics. Immunosuppression increases the risk of infection, and, therefore, the annual vaccination for patients on immunosuppressants has been proposed^[2]. Whereas the majority of patients suffering IBD will receive immunosuppressive therapy during the course of their disease, the ECCO consensus recommends annual vaccination since the disease was diagnosed^[2].

There is a live-attenuated influenza vaccine and also an inactivated type. The live-attenuated one is not recommended for patients on immunomodulators, but the trivalent inactivated influenza vaccine is not contraindicated in patients on immunosuppressants^[49].

Influenza vaccine seems to be less immunogenic in IBD patients, especially evidenced by a low serologic responses against the virus type B^[7,8,50,51]. For example, Mamula *et al*^[7] included 51 children with IBD and 29 healthy controls and found a significantly poorer immune response in IBD patients than in healthy controls. Furthermore, patients receiving infliximab and immunomodulators were less likely to respond to influenza vaccine antigens. These results were also confirmed by deBruyn *et al*^[8] in a study that included 60 children with IBD and 53 healthy controls

who received inactivated influenza vaccines, including both type A (H1N1 and H3N2) and type B. In this study, children with IBD showed a diminished response to the B component (53%) compared to healthy individuals (81%).

The negative effect of immunosuppression on the response to the influenza vaccine has been assessed in several diseases. For example, Cowan *et al.*^[52] observed lower immunogenicity of the vaccine in immunosuppressed kidney recipients than in healthy people. This diminished response seemed to be associated with a defective humoral and cellular response and with suppression of differentiation of B cells into IgG-secreting plasma cells supported by immunosuppressive therapy. A recent study by Bálint *et al.*^[53] showed that the administration of the vaccine in IBD patients (74% of whom were receiving immunosuppressive therapy) induced a decrease in serum IL-2 levels. Other immune-mediated and chronic viral diseases, such as rheumatoid arthritis, HIV, and common variable immunodeficiency, have been associated with an impaired immune response to the influenza vaccine, thus highlighting the importance of vaccinee immune status.

Genetic polymorphisms have also been associated with the response to influenza vaccination^[54].

In conclusion, despite the fact that the response to influenza vaccine appears to be diminished in IBD patients taking immunosuppressant drugs, the degree of response reached in most cases seems to be enough, so the annual influenza vaccination is recommended^[12].

Pneumococcal vaccination

Streptococcus pneumoniae is a pathological micro-organism that is able to cause serious infections, such as meningitis or pneumonia. Cohort studies have shown that one of the most prevalent infections in immunosuppressed patients with IBD is bacterial pneumonia^[55], maintaining these patients at high risk of invasive pneumococcal disease^[16,18]. Accordingly, it is recommended to administer, at least, one dose of the pneumococcal vaccine to all IBD patients^[2].

Two types of pneumococcal vaccine are available: the 23-valent polysaccharide vaccine and the conjugate vaccines (polysaccharides conjugated to proteins, such as diphtheria and tetanus toxoids, meningococcal outer membrane protein complex or protein D of *Haemophilus influenzae*). Both types of vaccines can be used in IBD patients, but most studies have focused on the 23-valent polysaccharide vaccine.

The immunogenicity of pneumococcal polysaccharide vaccination has been assessed in IBD patients. Study results suggested that IBD patients receiving immunosuppressants have significantly impaired postvaccination titers, while not immunosuppressed patients and healthy people do not and have similar response rates to one another. Moreover, patients on combination therapy (*i.e.*, taking more than

one immunosuppressant) had a lesser immune response to the pneumococcal vaccine than patients treated with only one immunosuppressive drug in monotherapy^[9,10,55]. As these data reflect that, somehow, immunosuppressant therapy influences the outcome of the 23-valent pneumococcal vaccine, it is advisable to administer the vaccine at diagnosis or at least 2 wk before starting any immunomodulatory treatment^[13,55]. A booster dose should be administered after 5 years^[2]. Despite the suboptimal response to vaccination among IBD patients receiving immunomodulators or biological drugs, the vaccine could still confer some degree of protection^[3].

Pneumococcal 23-valent vaccine is composed of polysaccharides that are T-cell-independent antigens, which do not induce immunologic memory. B lymphocytes are responsible for recognizing polysaccharides and secreting protective antibodies against pneumococcal bacteria (IgG and IgM). The phenotype of the B cells that react specifically against the 23-valent vaccine has not been fully identified, although, at least in young healthy people, most seem to be IgM⁺ memory B cells^[56]. In elderly people, however, the response to the 23-valent vaccine was mediated by switched memory B cells (IgM⁺) instead of IgM⁺ memory B cells^[57]. This "alternative" immunological mechanism that generates protection through switched memory B cells was also associated with decreased opsonophagocytic activity^[57]. People with low counts of IgM⁺ memory B cells (*e.g.*, the elderly or patients with common variable immunodeficiency) showed diminished efficacy of pneumococcal vaccine and increased susceptibility to infections caused by encapsulated bacteria, such as *S. pneumoniae*^[58,59]. Notably, IBD patients, even those who are not receiving immunomodulators, also have a lower proportion of circulating IgM⁺ memory B cells than healthy controls, probably owing to deficient spleen function^[60,61].

Other studies that have investigated the relevance of switched memory B cells in IBD patients have shown conflicting results. Di Sabatino *et al.*^[60] compared the percentage of circulating switched memory B cells between patients with IBD and healthy adults and found no significant differences. In contrast, Fallahi *et al.*^[62] found fewer switched memory B cells in children with Crohn's disease (but not in those with ulcerative colitis) than in healthy young adults vaccinated with a nonconjugate pneumococcal vaccine.

An increase in the proportion of IgM⁺ memory B cells has been observed in IBD patients who respond to anti-TNF drugs^[63]. This finding has been confirmed in patients with spondyloarthritis receiving anti-TNF therapy^[64]. To the best of our knowledge, no study has assessed the possible relationship between switched/unswitched memory B-cell counts, opsonization activity, use of immunosuppressants, and response to pneumococcal vaccine in IBD patients.

In contrast to vaccines that include only poly-

saccharides, conjugate pneumococcal vaccines have the advantage of inducing both humoral response and immune memory. However, despite their potential benefits in IBD patients, conjugate pneumococcal vaccines have been poorly studied.

Tetanus

Patients with IBD not vaccinated against tetanus or with unknown vaccination status should receive the primary series of tetanus vaccines (three doses). After the initial series, all patients should receive the booster every 10 years. Three studies have investigated the serological response to the booster vaccine in IBD patients and found conflicting results: two studies suggested an altered response^[65,66], while the third observed normal anti-tetanus antibody titers^[67]. Brogan *et al*^[65] suggested that the impaired response to the tetanus vaccine in IBD patients could be caused by a defect in the development of IgG-secreting plasma cells; however, this finding has not been confirmed elsewhere.

LIVE-ATTENUATED VACCINES

Measles, mumps and rubella

Since the vaccine against measles, mumps, and rubella is commonly administered in childhood, it is usually given before IBD is diagnosed. Vaccine can be administered in IBD patients not treated with immunosuppressant drugs and lacking immunity. Nevertheless, as this vaccine is generally given in most developed countries, the risk of acquisition of these infections is very low^[68].

Varicella and herpes zoster vaccinations

Varicella infection is generally a mild disease in children, but it can develop severe complications, especially in adults, leading to death in 20/100000 people^[69]. Immunity to varicella is usually acquired through infection during childhood^[18]; however, as this illness is very contagious, adults not immunized are at high risk of be infected. Since a third of infected immunocompromised patients have a disseminated herpes zoster disease^[69], it is recommended to confirm the seroprotection of IBD patients before the administration of an immunomodulator.

Local guidelines generally recommend the vaccination of children between the ages of 12 and 18 mo and administration of a booster dose at 11-12 years. Children with IBD not treated with immunosuppressant drugs should follow the same vaccination protocol^[2]. In the case of adult patients with IBD not immunized against varicella, it is recommended to administer the two-dose series of varicella vaccine at least 3 wk before starting any immunomodulatory therapy^[2]. Although recent studies show that this vaccine is effective and safe, even in immunosuppressed patients, data are still scarce. Given the potential risk of complications due to

the progression of the infection in immunocompromised adults, the benefits and risks of the varicella vaccine should be considered on an individual basis.

After resolution of the varicella infection, the virus stays latent within the spinal ganglion. The reactivation of the virus results in the Herpes zoster infection (shingles), that is developed in up to one in three people in the general population and in an higher rate among immunocompromised patients^[69].

A herpes zoster vaccine has been licensed in the United States. This vaccine is a live-attenuated strain of the varicella zoster virus, 14 times more potent than the single-antigen varicella vaccine, and it is suggested for people over 60 years in order to prevent and/or reduce the severity of herpes zoster complications^[70]. As little information is available regarding the safety and efficacy of the vaccine in immunocompromised patients, and immunosuppression can lead to a disseminated disease in case of infection, guidelines do not recommend the administration of the shingles vaccine in patients treated with anti-TNF drugs^[71] and suggest a window of 1-3 mo after initiating immunosuppressive therapy^[72-74]. Nevertheless, the Centers for Disease Control (CDC) and the Advisory Committee on immunization Practices (ACIP) stated that patients with lower levels of immunosuppression (≤ 0.4 mg/kg per week of methotrexate, ≤ 3 mg/kg per day of azathioprine, or ≤ 1.5 mg/kg per day of mercaptopurine) can tolerate attenuated herpes zoster-based vaccine. In fact, the risk of recurrence of varicella is low, even in profoundly immunosuppressed patients, as varicella-zoster immunity is well-maintained over time^[71].

In this respect, Zhang *et al*^[72] studied the incidence of herpes zoster disease after administering the live-attenuated vaccine in a cohort of 450000 patients with immune-mediated diseases (including IBD). The study concluded that the short-term risk of herpes zoster was not increased in vaccinated patients, independently of the prescription of anti-TNF therapy. Moreover, a decline in the incidence of herpes zoster over a median 2 years of follow-up was related to the vaccination^[72]. However, the proportion of vaccinated patients was small (1.2%), suggesting that further evidence is needed to confirm the safety of the vaccine in this population.

CONCLUSION

Patients with IBD are at risk of vaccine-preventable illnesses. The immunization status of patients with IBD should be verified, even with respect to routinely administered vaccines. It has been suggested that the response to vaccines in IBD patients is impaired owing to the immunological alterations generated by the disease and to the immunomodulatory treatments. The immunogenicity of hepatitis B, influenza, and pneumococcal vaccines is impaired in IBD patients,

whereas the response to papillomavirus vaccine seems to be similar to that observed in the healthy population. Data on the immunogenicity of tetanus vaccine in patients with IBD are conflicting. Studies assessing the response of patients with IBD to measles-mumps-rubella, varicella, and herpes zoster vaccines are scarce. The mechanisms involved in the altered response to vaccines in IBD patients remain unclear. Several HLA haplotypes have been associated with a higher risk of vaccination failure; however, whether these genetic factors cause deficient antigen presentation or diminished recognition by immune cells remains unknown.

Studies aiming to assess the response to vaccines in IBD patients and to identify the mechanisms involved in their immunogenicity are warranted. Understanding the alterations of the immune system of IBD patients is a key area in the development of more immunogenic vaccines for this particular group of patients and for other patients with immune-mediated diseases.

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