Review Article

Effects of Immunosuppressants on Immune Response to Vaccine in Inflammatory Bowel Disease

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Abstract

Objective: To evaluate the response rate to vaccination in different treatment groups (nonimmunosuppressants and immunosuppressants).
Data Sources: We completed an online systematic search using PubMed to identify all articles published in English between January 1990 and December 2013 assessing the effect of the response rate to vaccination in different treatment groups (with and without immunomodulators). The following terms were used: "inflammatory bowel disease (IBD)" OR "Crohn's disease" OR "ulcerative colitis" AND ("vaccination" OR "vaccine") AND ("corticosteroids" OR "mercaptopurine" OR "azathioprine" OR "methotrexate [MTX]") AND "immunomodulators."
Study Selection: The inclusion criteria of articles were that the studies: (1) Randomized controlled trials which included patients with a diagnosis of IBD (established by standard clinical, radiographic, endoscopic, and histologic criteria); (2) exposed patients received immunomodulators for maintenance (weight-appropriate doses of 6-mercaptopurine/azathioprine or within 3 months of stopping, 15 mg or more MTX per week or within 3 months of stopping; (3) exposed patients received nonimmunomodulators (no therapy, antibiotics only, mesalazine only, biological agent only such as infliximab, adalimumab, certolizumab or natalizumab or within 3 months of stopping one of these agents). The exclusion criteria of articles were that the studies: (1) History of hepatitis B virus (HBV), influenza or streptococcus pneumoniae infection; (2) patients who had previously been vaccinated against HBV, influenza or streptococcus pneumoniae; (3) any medical condition known to cause immunosuppression (e.g. chronic renal failure and human immunodeficiency virus infection); (4) individuals with positive hepatitis markers or liver cirrhosis; (5) patients with a known allergy to eggs or other components of the vaccines and (6) pregnancy.
Results: Patients treated with immunomodulators were associated with lower response rates to vaccination.
Conclusions: Immunomodulators may impair the immune response to vaccination in patients with IBD. Vaccination should be made at the time of diagnosis or before starting immunosuppressed therapy.

Key words: Crohn's Disease; Immunosuppressants; Inflammatory Bowel Disease; Ulcerative Colitis; Vaccination

Immune-suppressive Medications and Opportunistic Infections for Inflammatory Bowel Disease Patients

Inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease (CD) is chronic inflammatory bowel disorders in which an altered immune response and environmental triggering factors lead to chronic inflammation of the intestinal tract.[1] Patients with IBD are often placed on long-term immunosuppressants (corticosteroids, azathioprine, 6-mercaptopurine and methotrexate [MTX]) or antitumor necrosis factor (anti-tumor necrosis factor-α [TNF-α] agents such as infliximab, adalimumab and certolizumab) to minimize prolonged steroid use and in the case of relapse.[2,3] The immune-suppressive medications seem to be more effective than nonimmunosuppressive medications in increasing the chances of therapeutic response in patients with IBD.[4]

Immunosuppressive treatment is corticosteroids, immunomodulatory drugs (thiopurines, MTX or cyclosporine) and/or anti-TNF-α drugs 12 weeks before, or within 4 weeks after each dose of vaccine.[5] Prolonged and continued immunosuppression in patients with IBD can cause opportunistic infections than the general population and the outcomes of these infections may be more severe, or even fatal.[6] There are several published case reports of fatal vaccine-preventable infections with streptococcus pneumoniae, hepatitis B and varicella.[7] Recent North

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.152683

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American and European guidelines strongly recommended vaccination against potentially severe infectious agents, such as the pneumococcus pneumonia, influenza, and the hepatitis B virus (HBV) on the prevention of opportunistic infections.[8,9]

Immunosuppressants on Immune Response to Vaccination

Pneumococcal polysaccharide vaccine-23

Streptococcus pneumoniae causes up to 500,000 cases of pneumonia a year in USA.[10] It is the most common cause of community-acquired pneumonia. Pneumococcal pneumonia causes up to 25% of deadly infections in patients requiring prolonged immunosuppressive therapy.[11] Patients with IBD have an increased risk of pneumococcal pneumonia. The 23-valent pneumococcal polysaccharide vaccine (PPSV-23) contains up to 98% of the pneumococcal serotypes that cause pneumonia.[12] It reduces the morbidity associated with invasive pneumococcal disease in adults, especially those receive immunosuppressive medications with chronic medical conditions.[13] Patients with IBD are with chronic medical condition and often receive immunosuppressants, which meet the criterions for receipt of pneumococcal vaccination. Vaccination of PPSV-23, which results in a high rate of protection against pneumonia is thus strongly recommended. Vaccine effectiveness ranges from 56% to 81% in immunosuppressed individuals for the prevention of pneumococcal pneumonia. However, its protective effect shrinks markedly patients with IBD in immune depression.[14]

Fiorino *et al*. demonstrated that patients with CD who receive anti-TNF therapy combined with immunomodulator (s) have diminished pneumococcal antibody responses especially for serotypes 6B, 9V, 14F, and 19F, which are responsible for about 80% of invasive pneumococcal disease as compared with healthy controls and nonimmunosuppressed subjects with IBD. 88.6% (31/35) of the patients treated with mesalamine, 78.9% (15/19) of the patients treated with azathioprine, 62.5% (10/16) of the patients treated with combined immunosuppression therapy, 57.7% (15/26) of patients treated with infliximab, showed an adequate response to vaccination with PPSV-23.[15] However, in another randomized controlled trial, patients treated with infliximab plus MTX had no different response to vaccination versus the placebo plus MTX group.[16] Lee *et al*. found the serological response rate was 50.0% on anti-TNF alone; 58.0% on anti-TNF combined with an immunomodulator, which was much lower than that of patients on 5-aminosalicylate (78.4%).[17] In conclusion, anti-TNF therapy was a significant predictor associated with the inadequate seroconversion rate to PPSV-23 in patients with IBD. The PPSV-23 vaccination strategy should be optimized for patients at the diagnosis of IBD before anti-TNF therapy.

H1N1

Until August 2010, more than 214 countries had reported over 18,449 deaths of H1N1 influenza 2009.[18] The risk factors for severe infection due to H1N1 influenza include different chronic underlying medical conditions such as heart, renal, lung and liver disease, cancer, as well as immunosuppression.[19] The WHO identified immunosuppression and chronic medical conditions as specific risks for H1N1 influenza infection, which are relevant to IBD.[20] Patients with IBD represent more significant risk, particularly those on immunosuppressant medications and innate immune defects.[21] Vaccination against influenza is recommended for IBD patients according to published guidelines both in the US and Europe.[22]

Andrisani *et al*. found that the seroconvertion rate was lower in IBD patients than in the healthy control group, either on anti-TNF-α alone or combined with immunosuppressants. Geometric mean titer (GMT) of antibodies was significantly lower in patients on combined therapy versus those on monotherapy.[23] While Cullen *et al*. identified that the postvaccination GMTs were significantly lower in subjects on combination immunosuppression than in those receiving no immunosuppression. Furthermore, the fold increase in GMTs was significantly lower in those on combined immunosuppression compared with those on monotherapy immunosuppression.[24] Since patients with IBD who receive immunosuppressant medications always have a low serological response to H1N1 vaccine, a second dose of the vaccine in improving the seroprotection rate is worthy of future study.

Hepatitis B virus

About 370 million people are chronically infected with HBV world-wide. Totally, 1.5 million people die annually from its liver dysfunction caused by chronic sequelae.[25] In healthy adult populations, the serological response after standard vaccination schedules against HBV is >90%. Chronic disease and immunodeficiency are factors associated with a decreased response to HBV vaccine.[26] The hepatitis B surface (HBs) antigen vaccine was administered using the standard regimen (0, 1 and 6 months). After 1–3 months postvaccination, anti-HBs values >10 U/L were considered as a successful serological response to vaccination. In individuals with IBD, the prevalence of effective seroprotection against HBV is only 12.0%–48.9%.[27] In patients with IBD receiving immunosuppressive therapy, reactivation of chronic hepatitis B can lead to serious liver dysfunction.

Sempere *et al*. showed poor response to HBV vaccination in patients with IBD, especially those with long-term IBD progression and those on corticosteroid therapies.[28] Gisbert *et al*. identified that the response rate to the HBV vaccination was very low in IBD patients receiving anti-TNFs, even with a double-dose schedule. In another study, they found that the only factor associated with a higher risk of loss of anti-HBs was treatment with anti-TNFs.[29] Fiocchi observed that the polarization of the T-helper response varied in patients with IBD.[30] Since the hepatitis surface antigen antibody secretion requires coordination of T-helper cytokines,[31] a

different T-helper function may explain the poor response to HBV vaccination in patients with late IBD.[32] However, this hypothesis should be studied in future studies. As the duration of positive hepatitis surface antigen antibody (anti-HBs) titers after HBV vaccination remains unresolved, there are few data to support whether anti-HBs titers should be periodically monitored and whether booster vaccines should be administered.[33] However, because anti-HBs is likely to persist for less time in patients with IBD on anti-TNF-α alone or combined with immunosuppressants, postvaccination testing every 6–12 months is advisable.[34] Since the response rate of HBV vaccinations was significantly lower in IBD patients receiving immunosuppressive therapy and with active disease, vaccination should be given during remission and at immunosuppression-free times.

Hepatitis A virus

Hepatitis A does not cause chronic liver disease like hepatitis B or C, but acute fulminant hepatitis A may be associated with high mortality rates.[26] Park *et al*. identified that the seroconversion rate was significantly lower in patients treated with infliximab or adalimumab than in those not treated. In addition, there was no significant difference when comparing anti-TNF alone with anti-TNF and other immunosuppressants in seroconversion rates. They also showed that the anti-TNF therapy was the only factor, which is significantly associated with no seroconversion.[35]

Vaccines Indicated in Patients with Inflammatory Bowel Disease and the Best Time for Vaccination

Our review has identified numerous studies examining the relationship between treatment with immunomodulators and the immune response to vaccination, the majority of which find a lower immune response rate to vaccination in IBD patients treated with immunosuppressive therapies, especially biologics such as anti-TNF therapy as compared those without immunosuppressive therapies. When on immunosuppressive therapies, especially anti-TNF, the risk of opportunistic infections in IBD is particularly increased. It has been shown that factors that influence the effectiveness of vaccination includes the immune competence of the vaccine recipient.[36] Anti-TNF and immunomodulators such as azathioprine, 6-mercaptopurine, and MTX are increasingly used to treat patients with IBD.[37] Furthermore, continued and prolonged endogenous immunosuppression in patients with IBD can increase the risk of opportunistic infections, which may be fatal.[38] So, guidelines have been strongly issued on the indication of vaccines, such as influenza, the HBV, and pneumococcus for these patients under treatments immunomodulators of as primary prevention of infection.[39] However, as a reduction in immune response will influence the production of a specific antibody, vaccination under conditions of immunosuppression is not likely to be as effective.[40] In addition, immunosuppression level depends on the duration, intensity, and type of treatment the patient receives.[8] Although 86% of these patients were taking immunosuppressive medications, vaccination coverage is usually low.[26] Only 28% received annual influenza vaccinations and 9% had received pneumococcal vaccine.[35] Patients are considered to be immunodepressed when on treatment with immunomodulators for maintenance, so the best time to immunize patients in need of immunomodulators may be at the IBD diagnosis.[36]

Ideally, future studies should address these limitations. Studies investigating the effects of anti-TNF monotherapy or with immunomodulators on the response to the vaccines in patients with IBD would be conducted. Antibody titers for different serotypes should be measured, not only an overall type is obtained. A serological surveillance of response is recommended at 1 month following the last dose, or at 3 months after treatment.

Conclusions

In summary, our review suggests immunomodulators may impair the immune response to vaccination in patients with IBD. However, further clinical studies investigating the effect of anti-TNF monotherapy or combined therapy of anti-TNF and immunomodulators on the response to vaccinations are still warranted. Considering the mean time interval between baseline and postvaccine assessment, vaccination should be made at the time of diagnosis of IBD. Furthermore, antibody titers should be measured following each dose and regularly after the immunosuppressive therapy. We can use double antigen dose as initial vaccination to achieve better response rates for immunodepressed patients. These patients should receive a second complete schedule with double antigen doses if an adequate response is not developed.

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Received: 03-09-2014 **Edited by:** Yuan-Yuan Ji
How to cite this article: Cao Y, Zhao D, Xu AT, Shen J, Ran ZH. Effects of Immunosuppressants on Immune Response to Vaccine in Inflammatory Bowel Disease. Chin Med J 2015;128:835-8.
Source of Support: Nil. **Conflict of Interest:** None declared.