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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease

Preventing infective complications in inflammatory bowel disease

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Abstract

Over the past decade there has been a dramatic change in the treatment of patients with Crohn's disease and ulcerative colitis, which comprise the inflammatory bowel diseases (IBD). This is due to the increasing use of immunosuppressives and in particular the biological agents, which are being used earlier in the course of disease, and for longer durations, as these therapies result in better clinical outcomes for patients. This, however, has the potential to increase the risk of opportunistic and serious infections in these patients, most of which are preventable. Much like the risk for potential malignancy resulting from the use of these therapies long-term, a balance needs to be struck between medication use to control the disease with minimization of the risk of an opportunistic infection. This outcome is achieved by the physician's tailored use of justified therapies, and the patients' education and actions to minimize infection risk. The purpose of this review is to explore the evidence and guidelines available to all physicians managing patients with IBD using immunomodulating agents and to aid in the prevention of opportunistic infections.

Key words: Infection; Complications; Inflammatory bowel diseases; Immunosuppression; Anti-tumor necrosis factor agents

Core tip: In inflammatory bowel diseases (IBD) there is increasing use of immunosuppressives and the biological agents, which are being used earlier in the course of disease, and for longer durations. This, however, has the potential to increase the risk of opportunistic and serious infections in these patients, most of which are preventable. A balance thus needs to be struck between medication use to control the disease with minimization of the risk of an opportunistic infection. This outcome is achieved by the physician's tailored use of justified therapies, and the patients' education and actions to minimize infection risk. The purpose of this review is to explore the evidence and guidelines available to all physicians managing patients with IBD.

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INTRODUCTION

Patients with one of the inflammatory bowel diseases (IBDs), Crohn's disease (CD) or ulcerative colitis (UC), are at an increased risk of infection, which is partly inherent to the diseases themselves, but may also be due to the therapies used in their management. The pathogenesis of IBD is potentially secondary to an inappropriate in-

nate immune response to normal colonic flora and this may result in the lack of an appropriate immunological response to potential pathogens[1]. In the more severe cases of IBD, patients may suffer from concurrent malnutrition and can need radical surgical procedures, which can further compromise the patients' immunological responses[2]. The drugs required for disease control, such as the corticosteroids, immunological modulators like the thiopurines, methotrexate and cyclosporine, as well as the anti-tumor necrosis factor alpha (TNFα) medications, also have as their primary function the inhibition, and control, of immune system activity. Therefore, these can further reduce the immunological responses resulting in an increased risk of opportunistic infection.

The prevalence of opportunistic infections in IBD, however, is difficult to assess as this can vary markedly between countries but as they may result in mortalities within the IBD patient population their avoidance is of great importance[3-6]. As an example, the background risk of tuberculosis (TB) in Spain is high at 21/100000, where it is considered endemic and the risk of infection can increase by up to 90-fold in IBD patients receiving an TNFα medication[7]. By contrast there is a much lower background prevalence of TB in countries like the United States at 6.8/100000[8] and 0.9/100000 in the non-indigenous Australian-born population[9]. The risk to both the general population, and the immunosuppressed IBD patient, is thus vastly less in these countries and was demonstrated in an Australian and New Zealand study examining the prevalence of serious infections in IBD patients receiving a TNFα agent where not a single patient suffered from either primary, or reactivated TB, despite 3 patients receiving TB chemo prophylaxis due to a positive Quantiferon gold test prior to the initiation of TNFα therapy[9]

While there is much concern regarding the TNFα drugs, as they may result in reactivation of granulomatous infections, particularly TB[10], there is frequently less emphasis given to the other immunomodulating medications and whether they should also be regarded with caution, especially when used in combination with the TNFα therapies. The future of IBD medicine is, however, moving towards more biological medications (certoluzimab, golimumab, natalizumab and vedoluzimab) and the use of combination therapies. The risk to benefit ratio of these medications for the IBD patient thus needs to be continually assessed and monitored in order to give the best outcomes, much like the balancing act required to maintain IBD remission while minimizing the risk of cancers in these patients[11].

Many infections have been associated with the use of the IBD medications, however, some may be specifically due to the mechanisms of action of individual medications[12]. Patients on the thiopurine agents appear to be at greater risk of developing viral infections like cytomegalovirus (CMV), Epstein Barr virus (EBV) and varicella zoster virus (VZV), which is thought to be secondary to the effect of the thiopurine metabolites on T cells leading to the induction of apoptosis[12]. By contrast, macrophage function is primarily affected in patients receiving a TNFα agent and it has clearly been documented that these medications reactivate TB and thus a meticulous screening program is required for these patients prior to undergoing these therapies[10].

There is thus a definite risk of infections other then TB with the use of the IBD medications, but overall they appear to be uncommon. In the Australia and New Zealand study only 2.2% of the patient population receiving TNFα therapy suffered a serious opportunistic infection. Almost half of these cases, however, were on a combination of immunosuppressive therapies[9]. This is similar to the findings of one of the first studies investigating opportunistic infection rates undertaken at the Mayo Clinic. This investigation demonstrated that the use of steroids, thiopurines and infliximab all impact on the rate of opportunistic infections in IBD. It noted that steroid use alone increased the risk by 2.6 fold (95%CI: 1.4-4.7) but this, however, increased further to 12.9 fold (95%CI: 4.5-37.0) when 2 or more of these drugs were used in combination[13].

Despite how rare an opportunistic infection may be, however, the difficulty is in recognizing and treating them once they have occurred and the fact that they can result in significant morbidity and mortality. Prevention is thus certainly regarded as much better than cure in these situations. The prevention of opportunistic infections is, therefore, both the patient's and treating physician's primary goal and can be achieved through the use of multiple modalities that include vaccinations, chemoprophylaxis and education of the patients and clinicians. Each of these factors is vital for the successful implementation of appropriate guidelines for the best patient management[14].

DEFINITION OF IMMUNOSUPPRESSION

An immunocompromised patient is someone in whom there is defective phagocytic, cellular, or humoral immunity, which leads to an increased risk of opportunistic infection and/or infective complications[15,16]. While the presence of active IBD can itself lead to an increased risk of infections, independent of immunomodulating drugs, secondary to loss of the intestinal mucosal integrity, the IBD patient is not considered as immunocompromised *per se*. IBD patients are thus considered as being immunosuppressed primarily as a result of the therapy they receive and/or from the presence of malnutrition[16,17]. The ECCO Consensus guidelines outline the various IBD therapies, which classify a patient as being immunocompromised and include the following: (1) treatment with steroids (prednisone or its equivalent of > 20 mg/d, or 2 mg/kg per day if < 10 kg, for 2 wk or more, and within 3 mo of stopping); (2) treatment with therapeutic doses of a thiopurine or discontinuation within the 3 mo preceding; (3) treatment with methotrexate or discontinuation within the preceding 3 mo; and (4) treatment with a TNFα agent or discontinuation within the preceding 3 mo[16,17].

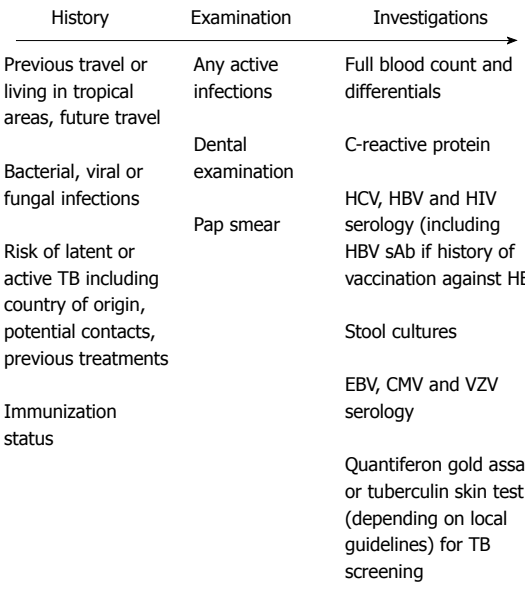

Figure 1 The patient pre-inflammatory bowel disease therapy work up. HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; TB: Tuberculosis; CMV: Cytomegalovirus; EBV: Epstein Barr virus; VZV: Varicella zoster virus.

VACCINATIONS

Understanding the role of vaccination in the IBD population is crucial for the patient, specialist and primary care physicians involved in patient care. As advances in medical therapies lead to healthier patients with a better quality of life, focus must shift from treating infection to maintaining well-being in our patients by the prevention of disease. Vaccination is one of those vital, but frequently forgotten, areas in infection prevention. Patients with IBD are at risk of the same vaccine-preventable illnesses as the general population, and since most IBD patients will be diagnosed after they have completed their childhood immunization schedules, and most will require immunosuppression therapy at some stage in their lifetime, the opportunity should be taken to explore each patient's immunization status at the time of the diagnosis of their IBD[15].

The institution of immunosuppressive and biological therapies also impact on which vaccinations a patient is allowed to receive and can also impact on the patient's response to vaccination with some studies demonstrating a lower response rate to vaccination once on these agents[18,19]. There is usually only a small window of opportunity in which to vaccinate the patient prior to the institution of treatment with an immunomodulatory agent. This must be taken advantage of in order to achieve the best possible patient outcomes. To date it is clear that the vaccination rates in the IBD populations are suboptimal and these need to be improve[20-23] and as there are now clear published international guidelines created to increase physician awareness of this issue and to improve vaccination rates and outcomes in the IBD population[16].

What to do at diagnosis

At the initial diagnosis, or first presentation, of an IBD patient, a thorough history, clinical examination and panel of blood investigations should be performed prior to commencing any immunosuppressive, or biologic, therapy. This should include a history of previous, and current, infections including viral [VZV, herpes simplex virus (HSV), human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus, EBV and CMV], bacterial (TB, pneumococcal and urinary tract infections) and fungal infections. A detailed vaccination and travel history is also crucial in further determining what vaccinations need to be recommended, boostered or checked. Figure 1 summarizes the patient pre-IBD therapy work up and Table 1 summarizes the vaccination recommendations based on current guidelines and evidence.

Once a patient is on a immunocompromising medication, inactivated vaccinations only are recommended and these are suggested in guidelines for immunocompromised patients who do not have an increase risk of infectious complications[24]. Live attenuated vaccinations need to be avoided in these patients (Table 1) as there is a risk that the administration of live vaccines to immunocompromised persons may result in adverse events, or vaccine-related disease, due to unchecked replication of the vaccine virus or bacteria. This is particularly noted for the measles-, mumps-, rubella[25,26] and VZV-containing vaccines[27] and for Bacille Calmette-Guérin (BCG) vaccine[28,29]. The risk of disease, however, varies for different vaccines and for different individuals so caution is required for the use of vaccination in the setting of immunocompromise. In significantly immunocompromised persons the use of almost all the live vaccines are contraindicated.

The live attenuated vaccinations include yellow fever, oral polio, BCG, measles-mumps-rubella, typhoid Ty21a, VZV, live attenuated influenza virus and herpes zoster (Centre for Disease Control, 2009). Ideally a patient should not be receiving an immunomodulating medication for at least 3 mo prior to vaccination and in the case of steroids, the patient should avoid use for at least a month. If a live vaccine must be given to an IBD patient, the recommencement of an immunomodulatory medication should be withheld for at least 3 wk[16].

RECOMMENDED VACCINATIONS - INACTIVE VACCINES

HBV vaccination

IBD patients who have less than 10 IU/L hepatitis B surface antibodies (anti-HBs) should be vaccinated against HBV according to the standard schedule (3 doses at 0, 1 and 6 mo) regardless of if they are immunosuppressed or not. When HBV vaccines are administered to a young healthy population, there is a > 95% protective seroconversion rate[30-32]. Yet studies in the IBD populations have revealed much lower rates of detectable anti-HBs post vaccination (33%-36%)[20,33], which could be attributable to

Table 1 Vaccines recommended in immunocompromised inflammatory bowel disease patients

Infectious disease	Vaccine type	Recommendation
Influenza	Inactivated trivalent virus	Recommended annually
Pneumococcal disease	23-valent purified capsular antigen	Recommended 5 yearly
Hepatitis B virus	Recombinant peptide	Recommended standard or double dose schedule
Human papilloma virus	Quadrivalent vaccine	In women according to local guidelines, standard schedule
Tetanus-Diptheria	Toxoid	Recommended in vaccinated patients 10 yearly
Measles-Mumps-Rubella	Live attenuated	Contraindicated
Varicella zoster	Live attenuated	Contraindicated
Yellow fever	Live attenuated	Contraindicated
Cholera	Oral live	Contraindicated
	Oral killed	Use with caution
Poliomyelitis	Oral live attenuated	Contraindicated
	Injectable inactivated	Recommended
Meningococcal	Conjugated polysaccharide	Authorised yet not recommended
	C polysaccharide combined	Authorised yet not recommended
Tuberculosis	BCG live vaccine	Always contraindicated

BCG: Bacille Calmette-Guérin.

an older age group[33] but also the use of biological therapy[18,34]. The use of a thiopurine medication, however, appears to have no negative impact on the efficacy of HBV vaccination but this may need further investigation[18].

Due to the significantly lower response rates to standard HBV vaccination in IBD patients, some studies have suggested a modified dosing regimen that doubles the standard antigen dose, given at 0, 1 and 2 mo. This was noted to result in 60% of the IBD patients having hepatitis B surface antigen levels > 10 IU/L[18]. Comparison between this and the standard vaccination regime has been studied in IBD where 148 patients were vaccinated with either the standard, or double dose, protocol with an anti-HBs of > 10 IU/L considered a successful response[35]. The seroconversion rate in the standard protocol group was 41% compared to a 75% seroconversion in the double dose protocol group. The advantage of the double dosing protocol was seen regardless of the use of immunosuppressive treatments and also was noted for achieving higher titres of anti-HBs with levels > 100 IU/L.

Considering the variability of HBV seroconversion, the best time to offer immunization is at the time of diagnosis prior to commencement of any immunomodulator therapy. Serological testing should then be undertaken after completion of the vaccination schedule (1-3 mo after the last dose) to determine if immunity was conferred[16,31,32]. If the standard protocol fails to achieve seroconversion, an additional vaccine can achieve a successful antibody response in between 25%-50% of patients and a complete second three-dose course has been shown to be successful in between 40%-100% of patients in non-IBD population studies[31,36].

Debate has also occurred around the ideal anti-HBs titre that should be reached post-vaccination in the IBD population. Post-vaccination anti-HBs titres of > 10 IU/L is considered to have conferred protection against infection in healthy subjects. This is long-term protection and relies on immune memory. In the immunocompromised patient, however, protection may be primarily reliant on the amount of circulating antibody rather than the immune memory. Thus titres > 100 IU/L in the United Kingdom are now considered as the new cut-off point for the vaccination to be considered as successful in the immunocompromised patient[32,37]. If these titres are not achieved after the 3-dose schedule, a 4th dose is then administered, or repetition of the full 3-dose series.

Influenza virus vaccination

Annual vaccination against influenza is recommended in IBD patients from the time of diagnosis[16]. Immunosuppressed patients have a higher risk of complications secondary to the influenza virus and there is greater associated morbidity and mortality[38]. The inactivated trivalent influenza vaccine comprises two type A subtypes (H1N1 and H3N2) as well as type B subtype. Studies have demonstrated mixed efficacy of the vaccine in the immunosuppressed population, mostly in paediatric IBD patients, which have demonstrated poor seroprotection results[39-42]. However, more recent data in adult IBD patients have demonstrated adequate seroprotection rates without exacerbation of intestinal disease[43]. Regardless of these findings, however, in most cases the immune response is adequate to warrant ongoing annual vaccination.

Pneumococcal vaccination

Streptococcus pneumoniae is the most common bacteria responsible for pneumonia and sepsis. IBD patients are also at increased risk of invasive pneumococcal sepsis[17,20]. Vaccination with the 23-valent strain is thus recommended to be administered every 5 years in the IBD population[16].

Again, as seen with other vaccines, effectiveness of this vaccine is diminished in patients on immunomodulating therapies, especially in combination, and therefore it should, ideally, be administered prior to commencement of such treatments[44]. Considering that the vaccine comprises 23 antigens to mount an immune response too, some degree of protection can be achieved and, therefore, it is considered worthwhile.

Human papilloma virus vaccination

The human papilloma virus (HPV) is the most common sexually transmitted infection[45]. This virus is oncogenic and can lead to cervical dysplasia with progression through to carcinoma[46,47]. While data is lacking of a clear link with this risk being heightened and the use of immunosuppression, and biological therapies, there is a theoretical risk of HPV-associated tumours in prolonged and combination immunosuppressing IBD therapy. Vaccination against HPV in IBD is thus advisable in the appropriate populations (young women ageing from 12 years to 26 years old) according to the local guidelines[16,48].

Tetanus and diphtheria

It is recommended that the general population should receive the tetanus, diphtheria and accellular pertussis vaccine every 10 years. This also holds true for patients with IBD. If the vaccination history is dubious then this should occur early within the IBD patient's course of treatment[16,49].

LIVE ATTENUATED VACCINES

Measles-mumps-rubella vaccination

Childhood immunizations against measles, mumps and rubella should be included in the initial history taking of the new IBD patient. In most developed countries there is a low risk of acquiring these infections as an adult due to herd immunity[50]. The evidence to support administration of the combined vaccine in patients prior to immunosuppressive therapy institution is also lacking and thus this is currently not a recommended vaccination by the ECCO guidelines.

Varicella vaccination

If patients with IBD have no history of having had varicella infection in childhood, serology should be checked and vaccination considered. Varicella infection in adults is more severe than in children, can be fatal and particularly severe if the patient is immunocompromised[51]. Unfortunately, this vaccination is a live vaccine, and thus IBD patients who are varicella naïve and are already immunosuppressed should not receive it. If, however, the patient is known not to be immune to varicella prior to IBD therapy, a 2-dose schedule should be given at least 3 wk prior to commencing an immunosuppressive medication[16]. Careful consideration of patients who might be at greater risk of varicella infection, such as children, teachers or health care workers, should guide the clinician in this decision.

CHEMOPROPHYLAXIS

Antibiotic prophylaxis has been a commonly used therapy in immunosuppressed patients to prevent opportunistic infections and the best example of this in IBD is for suspected latent, or active, TB. The TNF-α agents should be avoided in patients suspected of having latent, or active, TB until treatment for TB has been commenced and has been in effect for at least 4 wk in order to avoid reactivation of TB, or according to local guidelines[52-55].

Prophylaxis for *Pneumocystis jiroveci* with trimethoprim-supha-methoxazole[12] should also be considered in patients on combination immunomodulatory regimes, usually when they are receiving the combination of 3 agents that includes steroids[12,16,56], or in patients with low lymphocyte counts (< 600/μL)[57]. Alternative agents are aerosolized pentamidine, dapsone and atovaquone[58]. Data is lacking in this area and should be considered closely by the clinician on a case-by-case basis.

HSV

IBD patients with frequent and or severe recurrent HSV disease can be given oral anti-viral therapy to control these infections[16]. Considering most infections with HSV are mild and self-limiting, chemoprophylaxis is not recommended in IBD patients commencing immunomodulators. If HSV infection, however, disseminates during immunosuppressing therapy, then treatment with high dose antivirals and cessation of immunosuppressors is recommended[16].

HBV infection

HBV is a very common infection worldwide and is well known to reactivate in patients receiving immunosuppressive medications. This can result in significant morbidity and mortality, from liver function tests derangement through to fulminant hepatic failure and death unless anti-viral prophylaxis is given. This treatment strategy in preventing HBV flares is well established in patients with HBV-HIV co-infection and chronic HBV infected patients receiving systemic chemotherapy[59] and is becoming increasingly important in IBD patients particularly on combination immunomodulatory therapy and on the biologics[60]. There have been several case reports of fatal HBV flares in patients with IBD on immunosuppressant drugs[61-64] drawing concerns that the TNF alpha drugs may be involved in regulating HBV replication[65]. Patients who test positive for HbsAg should go onto anti-viral prophylaxis prior to commencing any immunosuppressive therapy. This is regardless of a detectable DNA viral load or not. Most recent guidelines suggest treatment with either entecavir or tenofovir over lamivudine due to fewer issues with developing viral resistance to these agents however most studies have been focused on lamivudine prophylaxis to date[59].

HIV infection

Prior to highly active anti-retroviral therapy (HAART), immunosuppressive agents, especially the anti-TNF drugs were contraindicated in HIV-infected IBD patients. Now that viral replication can be controlled and immune reconstitution achieved with the use of HAART, both the immunosuppressive and biologic agents can be used to treat IBD in patients who have a $CD4^+$ T lymphocyte count > 500/μL[66,67]. In those patients who are not on

HAART, but require immunosuppressive or biologic agents, then initiation of HAART should take priority, especially if $CD4^+$ T cell counts are < 500/μL.

EDUCATION

Patients need to be educated on how to recognize early symptoms of an opportunistic infection and to act quickly to get the required treatment if they are immunocompromised. Fever tends to be the most reliable, and sometimes the only, symptom for heralding the development of an opportunistic infection[68] and IBD patients should always seek medical advice and/or review should they be experiencing this, especially in combination with other symptoms and the use of immunomodulator therapies. In these circumstances, a thorough history, examination, and septic work up should be performed by the clinician to help isolate the source of infection and guide therapy. Of course fever can also be a sign of a flare and thus this should also be considered.

If the suspicion for an infective cause of a fever in the context of digestive symptoms is high, then vigilance to exclude infection should be the priority, rather than the escalation of IBD therapy. Stool cultures that also examine for *Clostridium difficile* (*C. difficile*) toxin and ova, cysts and parasites should be performed. It must also be noted that a single stool culture may only exclude 66% of infections. Multiple stool cultures are thus recommenced particularly for the excluding of *C. difficile* infection[69]. *C. difficile* is an increasing problem in immunocompromised patients and current estimates suggest that approximately 10% of IBD patients will develop symptomatic *C. difficile* infection at some point during the course of their lifetime[69]. This is important as it can lead to higher rates of colectomy and mortality.

If stool sample results are negative, an urgent colonoscopy or flexible sigmoidoscopy with colonic biopsies should be considered to assess for CMV colitis. This diagnosis is made on histological examination of biopsies taken at the interface of ulcers. Serum CMV PCR can also be performed but is not specific for active CMV disease[70].

CONCLUSION

In an era of increasing use of immunosuppressing medications in IBD and for longer durations, together with advocacy of the use of combination therapy, patients and their doctors need to be more vigilant about prevention and detection of opportunistic infections. IBD patients are at the same risk for vaccine-preventable illness as the general population. As IBD therapy can affect vaccine efficacy, then vaccination should be considered early in the course of disease and ideally prior to the commencement of any immunocompromising medication. The challenge for doctors is to balance the medical management of IBD, knowing the risks of individual therapies, and recognizing that prevention of opportunistic infections is as of equal importance. This usually requires the best use of one of the most precious commodities a doctor has with their patient, time.

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