Prevention of opportunistic infections in patients with inflammatory bowel disease and implications of the ECCO consensus in Belgium

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Abstract

In an era of increasing use of immunomodulator (IM) therapy, opportunistic infections have emerged as a pivotal safety issue in patients with inflammatory bowel disease (IBD). Today's challenge to the physician is not only to manage IBD, but also to recognise, prevent and treat common and uncommon infections. The recent European ECCO guidelines on the management and prevention of opportunistic infections in patients with IBD provide clinicians with guidance on the prevention, detection and management of opportunistic infections in patients with IBD. Proposals may appear radical, potentially changing current practice, but we believe that the recommendations will help optimise patient outcomes by reducing morbidity and mortality related to opportunistic infections in patients with IBD. In this ongoing process, prevention is far the first and most important step. Prevention of opportunistic infections relies on recognition of risk factors for infection, the use of primary or secondary chemoprophylaxis, careful monitoring (clinical and laboratory work-up) before and during the use of immunomodulators, vaccination and education of the patient. Special recommendations should also be given to patients before travel. Additionally, this paper discusses how the ECCO guidelines can be implemented in Belgium according to reimbursement legislation. (Acta gastroenterol. belg., **2010**, 73, **41-45**).

Introduction

The treatment of inflammatory bowel disease (IBD) has been revolutionised over the past decade by the increasing use of immunomodulators, mainly azathioprine (AZA)/6-mercaptopurine (6-MP) and methotrexate (MTX), together with the advent of biological therapies. Immunomodulators are being used more often and earlier in the course of the disease (1). The introduction of biologic agents, especially inhibitors of the key pro-inflammatory cytokine tumor necrosis factor alpha (TNF-α) initiated a new therapeutic era, and their use has grown continuously since their introduction in 1998 (2). However, with such intensified immunomodulation, the potential for opportunistic infections is a key safety concern for patients with IBD. Every experienced gastroenterologist can recall a case of disseminated varicella zoster, pneumocystis pneumonia or severe sepsis from an otherwise unheard of opportunistic pathogen in a patient with IBD on immunomodulators. A near disaster skilfully managed, perhaps, but a catastrophe for the patient, especially if such infection was preventable in the first place. So it is of the utmost importance that gastroenterologists are aware of the risks of opportunistic infections in IBD patients.

Opportunistic infections are defined as serious, usually progressive infections by a micro-organism that has limited (or no) pathogenic capacity under ordinary circumstances, but which has been able to cause serious disease as a result of the predisposing effect of another disease or of its treatment (3). Opportunistic infections pose particular problems for the clinician : they are often difficult to recognise and are associated with significant morbidity or mortality. Enhancing awareness and improving the knowledge of gastroenterologists about prevention, management and treatment of opportunistic infections are crucial elements to optimise patient outcomes. Prevention of opportunistic infections relies on recognition of risk factors for infection, the use of primary or secondary chemoprophylaxis, careful monitoring (clinical and laboratory work-up) before and during the use of immunomodulators, vaccination and education of the patient. Special recommendations should also be given to patients before travel. Implementing these preventive strategies may have a substantial impact on the organization of care and on current clinical practice (4).

Risk factors for infection

Predisposing risk factors enable the infection to develop and progress to an extent that is not otherwise seen (3). It is therefore mandatory to identify patients carrying those risk factors. Two categories of risk factors are defined : those that are external to the patient (immunomodulator therapy, exposure to pathogens and geographic clustering) and those that are inherent to the patient (age, malnutrition and co-morbidities).

Viral, bacterial, parasitic and fungal infections have all been associated with the use of immunomodulator therapy in IBD. No strict correlation between a specific immunomodulator drug and a certain type of infection has been observed. Furthermore, these drugs are commonly administered together, so the infectious event might be the consequence of cumulative immunosup-

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pressive treatment. Each immunomodulator carries an increased risk of infection, although to a varying degree that has not yet been quantified. Of fundamental importance is the observation that combination of immunomodulator therapy, especially with corticosteroids, is associated with an incremental increase in the relative risk of opportunistic infection (5).

Exposure to pathogens is a risk factor for opportunistic infection in the immunocompromised population. Living in an area where tuberculosis or other diseases such as histoplasmosis or coccidioidomycosis are endemic, inevitably increases the risk for contracting an opportunistic infection in the normal population, even-more in those who are on immunomodulator therapy (6). Avoiding close contact with pathogens and stays in endemic areas may be beneficial in reducing the risk of infection in IBD patients.

Although increasing age is without doubt a risk factor for infection in the general population, it is surprising that this was not found in many series, (7,8) although, a single case-control study of 100 patients identified age $>$ 50 as a predisposing factor (5). It is therefore of greatest importance to remain cautious when treating this subgroup of the IBD population, especially with anti-TNF therapy.

Malnutrition appears to be the major cause of decreased immune function worldwide and is a major risk factor for infection (9). Numerous factors contribute to malnutrition in IBD : anorexia, drug-nutrient interaction, malabsorption, inadequate intake, ileal resection and jejunal disease or resection (10). Better measures of nutritional status are the body mass index (BMI) and a formal nutritional assessment of intake and expenditure by a dietician. Since nutritional support can reverse the impact of malnutrition on impaired immune function, it is a practical measure to reduce risk of infection that should readily be implemented.

Underlying co-morbidities, unrelated to IBD, are also considered as independent risk factors for opportunistic infections (11). These conditions encompass chronic conditions of the heart, lungs, kidneys and liver, diabetes mellitus, chronic haematological diseases and splenic dysfunctions.

Primary and secondary chemoprophylaxis

Chemoprophylaxis is an effective and safe way of preventing infection during immunosuppressive use and is easily applicable for many pathogens such as *Mycobacterium tuberculosis, Pneumocystis jiroveci*, *Herpes simplex* virus, *Strongyloides stercoralis* and *Hepatitis B virus*. The European Crohn's and Colitis Organisation (ECCO) has developed guidelines for the prevention, diagnosis and treatment of opportunistic infections in IBD patients under immunomodulatory therapy (12).

Every patient with IBD is best evaluated at diagnosis to determine their risk of latent or active tuberculosis. In patients with *suspected latent or active tuberculosis*, anti-TNF alpha therapy should be postponed and anti-tuberculosis treatment given, according to national guidelines.

Primary prophylaxis for *pneumocystis jiroveci pneumonia* should be given for those patients on triple immunomodulators with one of these being a calcineurin inhibitor or anti-TNF therapy. Standard prophylaxis with co-trimoxazole is recommended (double- strength tablet daily 160-800 mg 3 times a week) although alternative regimens can be considered equivalent.

Frequent and/or severe recurrences of *herpes simplex virus disease* (usually oral-labial (HSV-1)) can be easily prevented with a daily therapy with oral acyclovir (400 mg twice daily) or valaciclovir. However, in Belgium, reimbursement of aciclovir is restricted to patients with frequent relapses of herpes with proven presence of HSV1 or 2 and valaciclovir is restricted to treatment of *Herpes zoster* infection of the ophthalmic nerve or in case of viral facial palsy.

Severe *strongyloidiasis* may occur in patients who have lived or travelled in endemic countries during the 30 years before onset. When these patients are treated with immunomodulators they should be screened for this disease. Serological testing, blood count including eosinophil count and multiple stool examination should be requested. Patients with positive screening tests and/or unexplained hypereosinophilia, as well as a history of travel or residence indicative of exposure to *Strongyloides stercoralis*, should be empirically treated, preferably with ivermectin (13) before starting immunosuppressive therapy. In Belgium, ivermectin is available in most university hospitals.

Immunomodulatory therapy carries the risk of *hepatitis B virus* reactivation (14). Therefore, ECCO guidelines advocate pre-emptive antiviral treatment with nucleotide/nucleoside analogues of chronic HBsAg+ carriers, best started 2 weeks prior to the introduction of corticosteroids, azathioprine, or anti-TNFα therapy and continued for 6 months after their withdrawal (12). Active Hepatitis B virus infection with high baseline HBV DNA levels ($>$ 2,000 IU/ml), should be treated until endpoints applicable to immunocompetent patients are reached, according to specific EASL guidelines (15). In Belgium, there is no reimbursement for any of the nucleotide/nucleoside analogues for prophylactic treatment of inactive HBsAg+ carriers. Reimbursement is restricted to chronic active *Hepatitis B virus* infection, with stringent criteria. Oral lamivudine is a relatively cheap drug and might therefore be used as pre-emptive treatment in order to follow the ECCO guidelines. Generic lamivudine may be in a near future the most appropriate option.

Clinical and laboratory work-up

Physical examination should include a search for systemic and/or local symptoms of infection. Dental status needs to be evaluated and appropriate dental care per-

formed. To reduce the risk of candida septicaemia, fungal infections such as oral and vaginal candidosis or intertrigo should be identified and appropriately treated. Gynaecological examination and cervical cancer screening should be systematically planned for women with IBD before and during treatment with immunomodulators (12, 16).

Ideally, baseline tests, potentially performed at diagnosis should include : neutrophil and lymphocyte cell count, C-reactive protein, urine analysis in patients with prior history of urinary tract infection or urinary symptoms, *varicella zoster virus* (VZV) serology in patients without a reliable history of varicella immunization, *Hepatitis B virus* and *Human Immunodeficiency Virus* (HIV) serologies, eosinophil cell count, stool examination and *strongyloides* serology (for returning travellers) (12).

Vaccination

Vaccine-preventable diseases are a major source of morbidity and mortality in patients with altered immune competence. Protection against a vaccine preventable illness is of great benefit to those patients at risk of complications of infections because of their immunecompromised state. For the abovementioned reasons, a vaccination program can reasonably be given for patients with IBD, preferably at diagnosis. Ideally, immunization status should be checked when the patient is first seen at the IBD clinic and a request made to the general practitioner for the vaccination record. Some vaccines (a minority) are attenuated live vaccines and are therefore contraindicated in immunocompromised patients. Reasons for early implementation of a vaccination program is based on the liberty to use any type of vaccine and on an anticipated higher rate of protective immunity in the absence of immunomodulatory drugs. Therefore, it is advised to start vaccination as soon as possible, at the time of diagnosis of IBD and before the introduction of immunomodulatory therapy (12). The routine vaccination program should be followed in patients with IBD according to national requirements for the general population. The Belgian guidelines can be consulted on the Superior Health Council website (http://www. health.fgov.be/CSH_HGR). Among others this includes (for adults) immunization against tetanus, diphtheria, pertussis, and poliomyelitis, with adequate boosters when necessary. Although immunomodulatory drugs may influence the response to vaccination, there is no place for routine measurement of the antibody response. Whether immunization will reduce the risk of infection in the IBD population in clinical practice would need large population based studies and will therefore be difficult to prove.

Five specific vaccines should also be considered for patients with IBD. These are varicella vaccine, hepatitis B vaccine, human papilloma virus vaccine, pneumococcal polysaccharide vaccine, and influenza vaccine (12). Two varicella zoster vaccines, both live-vaccine exist : the varicella vaccine and the zoster vaccine. Varicella vaccine should be considered in patients with no history of chickenpox or shingles, no prior immunization, and negative serology for varicella zoster. This represents a small minority of patients, since most of the population in industrialized countries will have been exposed to the disease in childhood. Varicella vaccine is a live vaccine and is contraindicated in patients receiving immunomodulatory drugs. A two-dose vaccination schedule (with ≥4 weeks between doses) is recommended for adults. In Belgium it is also reimbursed for adults with a chronic disease with longstanding corticosteroid therapy. The risk of reactivation of VZV infection in patients with prior history of varicella and treated with immunomodulatory therapy is increased and may be prevented using the zoster vaccine (Zostavax®). No recommendations are available for zoster vaccine in IBD patients, although it may actually be safe in patients treated with low doses of methotrexate or azathioprine (17). This vaccine is currently not available in Belgium.

Hepatitis B vaccine can be administered safely in patients with IBD using a three-dose immunization schedule. Patients treated with immunomodulatory therapy may have a suboptimal serological response. Therefore, routine testing for serological response is appropriate 1-3 months after completion of the full hepatitis B vaccination schedule. In individuals with a poor response, various alternative vaccination strategies can be applied and hepatologist's advice is most appropriate. Hepatitis B vaccination is recommended and reimbursed for children in Belgium since 1999 so most adolescents and adults younger than 25 years old are already vaccinated. Vaccination of adult IBD patients or immunocompromised patients is not reimbursed currently.

The human papilloma virus vaccine is a non-live vaccine that is best aimed at young female IBD patients. This vaccine has not been extensively studied in patients with altered immune competence and a definitive conclusion on efficacy in this subgroup of patients is lacking. In Belgium, immunomodulatory therapy is not part of the reimbursement criteria. The cost-benefit ratio of this vaccine should be discussed with the gynecologist. Seasonal influenza vaccine should be given once a year, especially in older IBD patients receiving immunomodulatory therapy. In Belgium the vaccine is reimbursed for patients under immunomodulatory therapy.

The 23-valent pneumococcal polysaccharide vaccine is also recommended, with repeat revaccination every 3 to 5 years. In Belgium the vaccine may be reimbursed for some patient depending on their additional health insurance system.

Travel-related vaccines include vaccines against hepatitis A, typhoid fever, yellow fever, Japanese encephalitis, meningococcal meningitis, tick-borne encephalitis, and rabies. Travelling to developing countries exposes IBD patients to the risk of a vaccine-preventable disease that might be more severe in the case of concomitant use of immunomodulators. Physicians caring for immuno-

compromised individuals should emphasize the need for expert travel advice, including a review of vaccination status, prior to travel to tropical and less economically developed countries. When possible, vaccination for travel should be started several months before the trip to allow time to assess the serological response and the need for additional boosters. The vaccine against yellow fever is a live vaccine and is therefore contraindicated in patients treated with immunomodulatory therapy. Such patients should be discouraged from travelling to countries in Africa and South-America where the disease is endemic, or at the very least made aware of the risks and alternative preventive measures (day time mosquito prevention) if they cannot arrange an alternative itinerary. IBD patients not receiving immunomodulators can safely receive live vaccines. Specific travel-related vaccines are not reimbursed by the health insurance in Belgium.

Education

Cases of listeriosis and salmonella infections have been described during treatment with TNF antagonists. It is recommended to avoid certain home made or artisanal foods such as unpasteurized milk, soft cheese, cold cuts of meat, hot dogs, and refrigerated paté, raw or undercooked eggs, poultry and meats. Advising patients to avoid eating high-risk foods when they start treatment with TNF antagonists may reduce the incidence of emerging opportunistic infections (12).

Travel

Travelling to economically developing countries poses some specific risks to patients with IBD. Recommendations should be discussed with an appropriate infectious disease specialist or with a specialised travel clinic. They include travel-related vaccines, prevention of insect bites and malaria, avoiding contact with *Mycobacterium tuberculosis* and guidance for traveler's diarrhea (12).

Conclusion

In view of the increasing use of immunomodulatory agents and of more aggressive therapies, patients with IBD and their physicians should acquire more knowledge and greater awareness of opportunistic infections. The challenge to the medical practitioner is not just the maximally efficient management of inflammatory disease, but also the prevention, recognition and treatment of common and uncommon infections. In this ongoing process, prevention is by far the first and most important step.

So what does all this mean fort the practising clinician ? Quite a lot, if recommendations are followed, but principally in the organisation of care rather than clinical management. It demands a scarce commodity-time for thought on the way care is organised and delivered for IBD, although once the process is established it will demand little effort. In addition, this manuscript is calling out for the governement to re-evaluate the current reimbursement criteria for preventive therapy of several of these opportunistic infections. Several of these preemptive therapies and vaccinations, as suggested in the ECCO guidelines, are currently not reimbursed in Belgium. Therefore, these preventive measures against opportunistic infections may be restricted to those IBD patients who can financially afford them. We believe that reimbursement should be available for these scientifically sound situations.

The question that might be asked about a preventive strategy for opportunistic infections is not so much why, but why not. Think of this when faced with a patient that has a life-threatening, preventable infection.

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