IBD REVIEWS REVIEW ARTICLE

Infections and malignancies associated with medical therapy on patients with inflammatory bowel disease

Ignacio J. Alfaro[1,2*]

[1]Departamento de Gastroenterología, Hospital Guillermo Grant Benavente; [2]Departamento de Medicina Interna, Facultad de Medicina,Universidad de Concepción. Concepción, Chile

Abstract

Inflammatory bowel disease (IBD) has become a global disease with a progressive increased in the prevalence and incidence in the past decades. Treatment has also changed in the past years evolving from steroids and aminosalicylates to an increase in the use of immunosuppressors and biological therapies that have revolution IBD therapy, improving patient's outcomes. However, some risks are associated with these therapies, mainly an increased number of opportunistic infections and also the appearance of malignancies. The objective of this article is to review the most relevant infections associated to IBD therapies and also the risk of malignancies described in literature. (IBD Rev. 2018;4:151-6)

Corresponding author: *Ignacio J. Alfaro, ignacioalfaroperez@gmail.com*

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Introduction

Medical therapy of both ulcerative colitis and Cohn's disease (CD) has evolved in the past decades with an increase use of immunomodulators and biological therapies. This change has provided better outcomes as a decreased on hospital admissions, surgeries, steroid use, and an increased number of patients on clinical and endoscopic remission, achieving a better quality of life.

However, higher immunomodulation is associated with side effects as opportunistic risk infections and malignancies.

The aim of this article is to review the most relevant infections and malignancies associated with treatment.

Corresponding author:
*Ignacio J. Alfaro
E-mail: ignacioalfaroperez@gmail.com

Infections

Hepatitis B virus infection

Approximately one-third of the world's population has serological evidence of past or

present infection with hepatitis B virus (HBV) and 350-400 million people are chronic HBV surface antigen (HBsAg) carriers[1]. Reactivation of vitreoscillu hemoglobin has been described associated with inflammatory bowel disease (IBD) therapy (corticosteroids, immunosuppressors, and tumor necrosis factor [TNF] inhibitors); in this scenario, all patients should be tested to asses infection or vaccine status. It is recommended that all seronegative should receive a vaccination and that due to the impaired efficacy in IBD anti-HBs titers should be measured 1-2 months after the last dose to confirm that levels higher than 100 IU/l have been achieved[2].

Patients with elevated baseline HBV DNA levels (higher than 2000 OU/mL) treatment with entecavir or tenofovir from 2 weeks before the beginning of the immunomodulators until 12 months after their withdrawal. ECCO guidelines recommend that in patients with elevated baseline HBV DNA levels (>2000 UI/mL) should continue antiviral therapies until endpoints applicable to an immunocompetent patient are reached[2].

In patients who are HBsAg negative, but anti-HBc and anti-HBs positive or in those with an isolated anti-HBc reactivation under IBD treatment may occur, but it rarely happens, on this scenario routine prophylaxes are not recommended, elevation of hepatic transaminases, HBV serology, and HBV DNA every 1-3 months should be performed[3].

Hepatitis C infection

Hepatitis C is a worldwide infection that causes both acute and chronic infection with prevalence in the most affected regions of 2%[4]. Despite efforts vaccine does not exist; however, new treatment regimens are curative in > 95%[5].

There are few cases of liver dysfunction's related to treatment, mainly steroids. The use of immunosuppressors and biological therapies does not seem to have a worsening in the context of treatment; however the ECCCO 2014 guidelines suggest the screening for hepatitis C[2]. Treatment of new regimens has been describe to be safe and successful, even in the context of patients under anti-TNF therapy[6,7], on this scenario, TNF inhibitors are not contraindicated and they should be not be discontinued[2].

Human immunodeficiency virus infection

The HIV belongs to the human retrovirus family; it is world spread infections that affect an estimated of 36.9 million of people with a global HIV prevalence of 0.8% among adults according to the world health organization.

There is a lack of evidence on the influence of IBD treatment on the natural history of HIV. Some case–control studies of azathioprine and TNF inhibitors demonstrate that neither of both worsened HIV course[8,9].

The current recommendation is that all patients that are going to be treated with immunomodulators or biological therapy must be tested for HIV infection. Evidence bases recommendation for therapy are not available, but in general, is accepted that antiretroviral therapy (ART) should be considered on patients with IBD and HIV and that immunomodulators or biological therapy should be stopped if there is no response to ART.

Mycobacterium tuberculosis infection

The world health organization reports that presently, one-quarter of the world's population is thought to be infected with *Mycobacterium tuberculosis* (TB), producing in 2016 a total of 1.3 millions of deaths, making this infection the number one cause of death from an infectious disease. However, the number of new cases has decreased since 2000.

Anti-TNF therapy increases the risk of TB infection, for this reason, TB risk evaluation must be performed before a TNF inhibitor is started with an evaluation of epidemiological risk factors, physical examination, chest X-ray, and tuberculin skin test (TST). Interferon-gamma

release assay (IGRA) complement TST and is preferred in BCG immunized patients.

Latent TB diagnosis should be performed on patients without clinical or radiological evidence of an active TB and a positive TST (≥ 5 mm) or IGRA.

In patients diagnosed with latent TB a complete therapeutic regimen because chemoprophylaxis decreased the number of cases active TB[10,11].

The main regimen is based on isoniazid for 6-9 months with a ≥ 60% of protection[12]. Another option is rifapentine and isoniazid once a week that is effective with a low rate of hepatotoxicity[13].

Cytomegalovirus infection

The majority of primary infections with CMV are asymptomatic. Clinically apparent infections may present as a mononucleosis-like syndrome, but can affect virtually any organ[14].

In patients treated with immunosuppression, subclinical reactivation of CMV is often associated and in some cases, CMV disappears without antiviral therapy[15,16]; on this scenario, perform screening for sub-clinical CMV infection in IBD patients is not indicated.

The main indication of CMV screening is in patients with a severe steroid-refractory course; on this patients, CMV has been reported in up to 36% of patients[17]. The most used techniques for CMV diagnosis are histopathology, immunohistochemistry, and PCR and in patients with CMV disease confirmed that the usual treatment is ganciclovir for 2-3 weeks.

Influenza virus

There are two types of influenza virus that cause human epidemics: type A and type B that spreads around the world in yearly outbreaks resulting in about 3-5 million cases of severe illness and about 250,000-500,000 deaths according to the world health organization[18]. Immunosuppression is, generally, considerate as a risk for severe influenza infection; however, the incidence on IBD patients under immunomodulators seems not to be greater[19,20].

Vaccination is the most effective measure for preventing infection, and IBD patients on immunomodulators are candidates to perform an annual trivalent or quadrivalente inactivated vaccine. A lower efficacy of vaccination should be taken into account in patients undergoing immunosuppressive or anti-TNF treatment[21,22].

To reduce complications early use of antiviral therapy is recommended in patients with confirmed or suspected infection[23] (Table 1).

Malignancies

Immunosuppressors

Thiopurines

The standardized incidence ratio of lymphoma among patient's users of thiopurines is significantly increased; the three types associated are post-transplant-like lymphoma, post-mononucleosis lymphoma, and hepatoesplenic T-cell lymphoma[24]. It has been describe that this risk is higher males under 30 and patients over 50 years[25] and also that thiopurines may increased the risk of myelodysplastic syndromes and acute myeloid leukemia[26].

IBD patients exposed to thiopurines are also at risk for non-melanoma skin cancer (NMSC) that has been attributed to increased UVA-induced DNA damage, increased production of reactive oxygen species in skin epithelial cells[27-29].

Others immunosuppressors

There is no evidence that report an increased risk of cancer in patients treated with both methotrexate and calcineurin inhibitors[24].

TNF inhibitors

Evidence supported that anti-TNF is safe drugs and that the use of this drugs alone

Table 1. Recommendation for patients that are going to be treated with immunomodulators or biological therapies

Infection	Screening	Vaccination	Treatment
VHB	Recommended	Recommended	Recommended before, during and at least 12 months after immunomodulatory treatment has ceased in patients with Chronic HBV infection. Patients with higher HBV DNA levels should continue treatment
VHC	Recommended	Not available	Effective on IBD patients under therapy
VIH	Recommended	Not available	HAART should be considered on patients with IBD
Cytomegalovirus	Not necessary	Not available	In cases of severe steroid resistance with CMV detected in the mucosa treatment with ganciclovir during 2-3 weeks is recommended
Influenza	Not necessary	Annually	Early treatment on immunosuppressed patients
Mycobacterium tuberculosis	Recommended	Not recommended	Latent infection should be treated

HBV: hepatitis B virus, IBD: inflammatory bowel disease, CMV: cytomegalovirus, HAART: highly active antiretroviral therapy.

does not increased the risk of cancer at long term[30]. The use of a TNF inhibitor in patients with IBD has been associated with skin cancer. In the case of NMSC, the evidence is contradictory, and the association cannot be confirm[27,31,32]. Instead, TNF inhibitors have been describe as an indepently risk factor for melanoma in some studies[27,30].

Vedolizumab (VDZ)

VDZ binds to α4β7 integrin; a glycoprotein expressed on circulating B and T lymphocytes, inhibiting selective trafficking of gut-homing CD4+ T lymphocytes through addressing cell adhesion molecule 1.

In the registration trials malignancy was reported in 1/504 placebo-exposed patients and in 18/2830 patients with VDZ exposure, of those 6 cases were gastrointestinal malignancies, 5 were dermatological cancer, 2 breast cancers, 2 pulmonary, 1 B-cell lymphoma, and 2 genitourinary malignancies, most of them with history of previous treatment with thiopurines and another biological agent[33]. Adjusted comparisons between anti-TNF therapy and VDZ using data from registration trials and placebo as the common comparator did not reach significance (odds ratio: 0.87; 95% confidence interval: 0.26-2.88)[34].

With the evidence available there is no potential risk described for any neoplasia related to VDZ use[35,36].

Ustekinumab

Ustekinumab is a fully human monoclonal antibody directed against the p40 subunit of interleukin (IL)-12 and IL-23, its efficacy and safety were initially proved in patients with psoriasis and psoriatic arthritis where a similar number of NMSC was reported[37].

In the long-term follow-up studies on psoriasis, the pattern of NMSC was similar to that observed in psoriasis clinical trials of other biologics and the rates of malignancies other than NMSC in ustekinumab-treated patients were compared with the expected rates in the general population[38,39].

Both UNITI 1 and 2 trials confirmed the efficacy of ustekinumab in patients with Crohn's disease and that this biologic agent appears safe, with no increased risk of infectious or malignant complications[40] (Table 2).

Table 2. Malignancies associated with inflammatory bowel disease therapies

Treatment	Malignancies associated
Thiopurines	Lymphoma Nonmelanoma skin cancer
Methotrexate	Not reported with the evidence available
Calcineurin inhibitors	Not reported with the evidence available
TNF inhibitors	Melanoma
Vedolizumab	Not reported with the evidence available
Ustekinumab	Not reported with the evidence available

TNF: tumor necrosis factor.

Conclusions

IBD therapy is evolving, and in the past years, new therapeutic drugs are available. Side effects are a concern, but in general, the safety profile of the old and new treatments is good. There is an association with some infections and some malignancies, so on this scenario prophylactic measures and continues monitorization of our patients must be perform to minimize risk's associated to therapy.

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