Predicting, Preventing, and Managing Treatment-Related Complications in Patients With Inflammatory Bowel Diseases

Laurent Beaugerie, Jean-François Rahier, Julien Kirchgesner

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Short title: Management of treatment-related complications in IBD

Laurent Beaugerie (1), Jean-François Rahier (2) and Julien Kirchgesner (1)

(1) Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpital Saint-Antoine, Department of Gastroenterology, F75012, Paris, France.

(2) Université catholique de Louvain, CHU UCL Namur, Department of Gastroenterology, 1 Avenue Dr G Thérasse, 5530, Yvoir, Belgium

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Abbreviations used in this paper:

ALT, alanine aminotransferase ;

CT, computed tomography

EBV, Epstein-Barr virus;

HLH, hemophagocytic lymphohistiocytosis;

IBD, inflammatory bowel disease;

JAK, Janus kinase

OI, opportunistic infection;

SMPC, summary of product characteristics

TNF, tumor necrosis factor;

TPMT, thiopurine-methyl-transferase;

VZV, varicella zoster virus;

Corresponding author: Prof. Laurent Beaugerie, Service de Gastroentérologie et Nutrition, Hôpital Saint-Antoine, 184 rue du faubourg Saint-Antoine, 75571 Paris CEDEX 12, France. Tel: +33 1 49 28 31 71, Fax: +33 1 49 28 31 88

E-mail: laurent.beaugerie@aphp.fr

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ABSTRACT

Risk of complications from specific classes of drugs for inflammatory bowel diseases (IBD) can be kept low by respecting contra-indications. Patients with IBD frequently develop serious infections, due to the disease itself or its treatment. At the time of diagnosis, patients' vaccination calendars should be updated according to IBD guidelines—live vaccines should be postponed for patients receiving immunosuppressive drugs. Opportunistic infections should be detected and the vaccine against Pneumococcus should be given before patients begin immunosuppressive therapy. Thiopurines promote serious viral infections, in particular, whereas tumor necrosis factor (TNF) antagonists promote all types of serious and opportunistic infections. Severe forms of varicella can be prevented by vaccinating seronegative patients against varicella zoster virus. Detection and treatment of latent tuberculosis is mandatory before starting anti-TNF therapy and other new IBD drugs. Tofacitinib promotes herpes zoster infection in a dose- and age-dependent manner. Physicians should consider giving patients live vaccines against herpes zoster before they begin immunosuppressive therapy or a recombinant vaccine, when available, at any time point during treatment. Risk of thiopurine-induced lymphomas can be lowered by limiting the use of thiopurines in patients who are seronegative for Epstein-Barr virus (especially young men) and in older men. The risk of lymphoma related to monotherapy with anti-TNF agents is still unclear. There are no robust data on carcinogenic effects of recently developed IBD drugs. For patients with previous cancer at substantial risk of recurrence, physicians should try to implement a pause in the use of immunosuppressive therapy (except in patients with severe disease and no therapeutic alternative) and prioritize use of IBD drugs with lowest carcinogenic effects. Finally, sun protection and skin surveillance from the time of diagnosis are recommended.

Key words : ulcerative colitis, Crohn's disease, side effect, infliximab

Crohns' disease and ulcerative colitis are lifetime diseases. Maintenance treatments that are currently used include anti-inflammatory drugs that, with the exception of 5-amino-salicylates, have immunosuppressive properties. All IBD drugs that lead to sustained control of intestinal inflammation in individual patients are potentially able to reduce the incidence of IBD-related infections or inflammation-related cancers.[1] In return, all IBD drugs may provoke drug class-specific complications, and all immunosuppressive IBD drugs may promote infections and malignancies. Some safety signals have been identified during drug development[2] or in the early postmarketing era.[3] Others are suspected through postapproval case reports[4] or dedicated pharmaco-epidemiological studies,[5] sometimes several decades after approval of the drugs.[6] This sole observation should lead to a precautionary principle in the use of new IBD drugs. Regarding established risks, we focus here on preventive measures when they are possible. We also suggest a limited use of some IBD drugs in high-risk settings when therapeutic alternatives are available. However, as a general rule, IBD drugs are safe if prescribers are familiar with the contraindications and at-risk situations, and the benefits outweigh the risks.[1]

Drug class-specific complications

Simple clinical intolerance (nausea, headache) and organ damage may both lead to treatment withdrawal. We here consider drug complications as organ damage that may be life-threatening. Prediction, prevention and management techniques for main drug class-specific complications associated with the use of maintenance IBD drugs[7–10] are listed in Table 1. Prediction is currently limited to the detection of a genetic predisposition to thiopurine-induced myelosuppression.[11,12] In patients with established genetic susceptibility related to TMPT or NUDT15 variants, treatment should be started with low or very low doses according to their genetic status. Prevention of complications relies on the consideration of contraindications related to a personal and/or family history of organ damage. Early detection relies mainly on the

implementation of biological drug monitoring that is recommended by drug agencies in summaries of product characteristics.

Serious infections

Risks levels and patients at risk

Infections should be stratified according to severity. Serious infections are generally defined as infections that require hospitalization or intravenous antibiotics. Serious infections may be life-threatening in contrast with benign infections. Opportunistic infections (OIs) are life-threatening infections caused by microorganisms that take advantage of altered immunocompetence and cause disease where they ordinarily would cause either no disease or mild illness in cases of immunocompetence. Several pathogens cause OI, and the definition of OI differ across studies.[13,14]

Among the IBD population, the incidence rate of serious infections ranges between 10 and 100 events per 1000 person-years,[13–15] which is more than ten-fold higher than that of OIs.[13] The mortality rate is approximately 4% among patients with serious infections.[1]

Generally, serious infections related to uncontrolled IBD activity are more frequent than serious infections that may be purely attributed to IBD drugs.[1] There is an increased risk of all infections in patients exposed to corticosteroids and/or anti-TNF agents, but anti-TNF agents promote markedly bacterial and fungal opportunistic infections, such as *Legionella pneumophila* infection, particularly in older patients[13], and tuberculosis (Supplementary Table 1).[3] The excess risk related to thiopurines relates mainly to viral infections. Notably, primary cytomegalovirus, varicella-zoster virus (VZV), and Epstein-Barr virus (EBV) infections can be severe and/or cause hemophagocytic lymphohistiocytosis (HLH). HLH is mainly related to primary EBV infection, irrespective of gender and age.[16,17] The combination of thiopurines and anti-TNF agents exposes patients to higher risks of serious and opportunistic infections than does anti-TNF monotherapy,

which itself exposes patients to higher risks of serious infections as well as mycobacterial and opportunistic bacterial infections than does thiopurine monotherapy.[13]

Data from randomized clinical trials do not suggest an increased risk of infections with vedolizumab, except for a trend towards an increased incidence of *Clostridium difficile* infections,[18] but more real world data are definitively needed. There is no signal of excess infections related to the use of ustekinumab trials in IBD, and no excess risk of infection was reported in psoriasis.[19] Exposure to Janus kinase (JAK) inhibitors is associated with an increased risk of various infections, mainly herpes zoster. Based on data from randomized clinical trials of tofacitinib in ulcerative colitis,[20] the absolute risk of herpes zoster in patients aged older than 65 years is 95.5 events per 1000 person-years.[20] Increasing age and Asian race are also risk factors of herpes zoster.

Beyond the specific risk profile of each drug class, patient characteristics impact the risk of infections. First, IBD itself is associated with an increased risk of pneumococcal infection[21] and herpes zoster,[22] suggesting that vaccination strategies for these infections should be considered at IBD diagnosis. IBD activity contributes to this increased risk, since disease activity has been associated with an increased risk of serious infections.[15] Disease activity may also lead to malnutrition, which is a risk factor for infection, notably central venous catheter-related infection in cases of parenteral nutrition. Age is one of the strongest risk factor for infections[23] and is a surrogate marker of age-related comorbidities, with incidence rates of serious infections that are 2- to 3- fold greater and higher mortality rates (10%) in patients 65 years or older compared with younger patients.[13]

Prevention strategies

Prevention of OI is based on the recognition of risk factors for infection, use of primary prophylaxis, clinical and laboratory work-up before starting immunosuppressive therapy, advice and education provided to the patient, and a vaccination program. Despite these preventive

measures, serious infections regularly occur and require specific measures both to control the infection and to manage immunosuppressive therapy. Finally, following an infectious event, secondary prophylaxis can be appropriate in some patients.

Primary and secondary prophylaxis

In patients with suspected latent or active tuberculosis, anti-TNF therapy should be postponed and anti-tuberculosis treatment should be given according to national guidelines. In countries where tuberculosis is endemic, focused clinical examination combined with detection tests should be performed when the diagnosis of IBD is considered. The accuracy of interferon gamma release assays and tuberculin skin tests in diagnosing latent tuberculosis in immunocompromised IBD patients is lower than in immunocompetent adults.[24,25] For this reason, testing should be performed at the diagnosis of IBD and repeated prior to treatment with biologics. Primary prophylaxis for *Pneumocystis jiroveci* pneumonia should be given to patients on triple immunomodulators with one of these being a calcineurin inhibitor or anti-TNF therapy. Standard prophylaxis with cotrimoxazole is recommended (double- strength tablet daily 160-800mg 3 times a week).[26] Cotrimoxazole is the drug of choice for therapy and drug allergies should be documented before resorting to alternative therapies such as aerosolized pentamidine or atovaquone. Frequent and/or severe recurrences of herpes simplex virus disease can be prevented with a daily therapy with oral acyclovir or valaciclovir. Severe strongyloidiasis may occur in patients who have lived or travelled in endemic countries (i.e., South-East Asia, Latin America, Sub-Saharan Africa, and South-East USA) during the 30 years before onset. These patients should be screened for systemic hypereosinophilia, and serological testing and stool examination should be performed. 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 before starting immunosuppressive therapy.[27]

A severe Hepatitis B flare might arise during immunomodulator treatment. In patients who are hepatitis B virus (HBsAg+) carriers, prophylactic antiviral treatment with nucleotide or nucleoside analogues is recommended, best started 2 weeks prior to the introduction of steroids, azathioprine, or anti-TNFα therapy, and continued for 12 months after their withdrawal.[26] This strategy has been proven effective in reducing the rate of liver dysfunction in IBD patients who are chronic HBsAg+ carriers.[28] Prebiological testing for HBV is regularly enxpanded to HCV testing although no specific chemoprophylaxis regarding Hepatitis C infection is recommended. The immunomodulators and biologics are not globally contraindicated in case of active hepatitis C virus (HCV) infection and the decision depends on the severity of IBD and the stage of liver disease. An acute HCV infection should be treated according to standard practice without stopping immunosuppressive therapy.[26]

Clinical and laboratory work-up

A general physical examination and laboratory work up must be performed on diagnosis and are summarized in Table 2.

Education

Cases of listeriosis and *Salmonella* infections have been described in patients treated with anti-TNF therapy. Recommendations have been made to avoid certain foods such as those made from unpasteurized milk, soft cheese, cold cuts of meat, hot dogs, and refrigerated pâté, as well as raw or undercooked eggs, poultry and meats. Advising patients to avoid eating high-risk foods when being treated with anti-TNF agents may reduce the incidence of these OI.

Vaccination

Vaccine-preventable diseases are a major source of morbidity and mortality in immunocompromised patients. Patients with IBD are immunocompromised, mainly because of the immunomodulatory medications they take. It is important to remember that even the influenza virus can cause morbidity and mortality in young IBD patients.[29] Therefore, routine and specific immunizations are important to consider in this population. A low vaccination rate

has been reported in IBD patients because of the lack of awareness of the risk involved, the fear of side effects or the cost of vaccines.[30] Gastroenterologist and general practitioners must join forces to offer a vaccination strategy.

When should vaccines be administrated?

Vaccination is best implemented at an early stage of the disease. Ideally, the 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. The vaccination plan should be adapted to the patient and his socio-professional and familial situation. Thus, particular attention will be given to protecting a worker in a medical or prison environment against hepatitis B, while the same vaccine may not be offered to a sedentary and elderly patient. Special attention should also be given to patients working in the early childhood and education fields.

There is a risk of disseminated infection associated with the use of live vaccines in immunocompromised patients. The most currently used live vaccines are measles-mumps-rubella, yellow fever, and varicella zoster. Live-attenuated vaccines are contraindicated in IBD patients exposed to IBD drugs with high immunosuppressive impact (see the Table 2 footnote).. Live-attenuated vaccines should be avoided within the 3 months after immunosuppressants have been stopped. According to certain experts[31], this delay may be reduced in cases of low levels of immunosuppression, One month is sufficient if corticosteroids are used alone. Immunosuppressive therapy can be reintroduced 3 weeks after the time of a live vaccine injection.[26] Live-virus vaccines are probably safe in patients on <20 mg prednisone daily, or even on higher doses provided they have been administered for a period of less than 14 days. It is still unclear whether the use of live vaccines is safe in patients exposed to vedolizumab or ustekinumab. Patients who are not exposed to immunosuppressive therapy should be considered similarly to any healthy patient regardless of the vaccine being considered.

What type of vaccine for which type of patients?

A routine vaccination program should be followed in patients with IBD according to national requirements[26,32]. This includes (for adults) immunization against tetanus, diphtheria, pertussis, and poliomyelitis, with adequate boosters when necessary. Five specific vaccines should also be considered for patients with IBD (Table 3). These are varicella vaccines, hepatitis B vaccines, human papilloma virus vaccines, pneumococcal vaccines, and influenza vaccine. The varicella vaccines should be considered in patients with no history of chickenpox or shingles, no prior immunization, and negative serology for varicella zoster. The varicella vaccine is a live vaccine and is contraindicated in patients receiving immunosuppressive drugs. A two-dose vaccination schedule (with ≥4 weeks between doses) is recommended for adults. For prevention of herpes zoster (shingles), two vaccines are available in some countries: Zostavax® is a live attenuated vaccine whereas Shingrix® is a non-live recombinant vaccine that can be used preferably in immunocompromised patients. The latter is the preferred vaccine and is recommended in any patient aged 50 years and older in the U.S., regardless of immunocompromising status. Hepatitis B vaccine can be administered safely in patients with IBD using a three-dose immunization schedule. Patients treated with immunosuppressive therapy may have a suboptimal serological response. Therefore, routine testing for serological response is appropriate 1–3 months after hepatitis B vaccination. In individuals with a poor response, an additional booster dose may be required. The human papilloma virus vaccine is a nonlive vaccine that is best aimed at young IBD patients. Influenza vaccine should be given once a year, especially in older IBD patients receiving immunomodulatory therapy. Pneumococcal vaccines with both the 13-valent pneumococcal conjugate vaccine (PCV13) and the 23-valent pneumococcal polysaccharide vaccine (PPSV23) are also recommended, with a single revaccination after 5 years for the polysaccharide vaccine.

Numerous studies have shown the effectiveness and safety of vaccination in patients with chronic immune-mediated diseases. These studies show that the majority of immunocompromised patients develop antibodies, but sometimes at lower titers than in the

general population and that vaccination does not alter either the course or the clinical activity of the disease.[33,34] It has also been shown that the immunological response to vaccination is sometimes decreased in patients exposed to immunosuppressive therapy.[35–37]

How to treat IBD after a serious infection

Management of infection in IBD depends on the type and severity of the infection. Advice from an infectious disease specialist should be sought in cases of severe infection with unusual pathogens. In the case of minor infection (rhinitis, upper respiratory tract infection, etc.) with no high grade fever and no risk of disseminated disease, it is unnecessary to withdraw immunomodulators. However, in cases of risk for disseminated or uncontrolled disease (listeriosis, cerebral abscess, disseminated tuberculosis, shingles, pneumonia, encephalitis, etc.), high-grade fever and infection with an established mortality risk, withdrawal of immunomodulators is advised. The decision to resume immunosuppressive treatment is made on a case-by-case basis and a multidisciplinary approach. Management of each specific infection is detailed in the European consensus.[26]

Cancers

Established risks and gap of knowledge (Table 4)

There is a slight excess risk of dying of cancer in patients with Crohn's disease or ulcerative colitis compared with age and gender-matched individuals from the general population.[38] The majority of IBD-related cancers are digestive cancers related to uncontrolled IBD inflammation and not purely attributable to IBD drugs.[39] Most of individuals with IBD will develop sporadic cancers and should participate in screening programs (breast and uterine cervix cancer). Some unusual forms of EBV-related posttransplant-like lymphomas may develop selectively in patients with IBD exposed to immunosuppressive drugs,[40] which suggests an iatrogenic origin. In general, only pharmaco-epidemiology can prove that a given treatment promotes cancers.

Knowing that the incidence of individual cancers in the general population does not usually exceed 1/1000 patient-years, the assessment of an excess cancer risk due to a new IBD drug requires a total observation time of 20,000 to 50,000 patient-years. This explains why it took 20 years of routine use of thiopurines to demonstrate that this drug class promotes, as in the posttransplant state, EBV-related lymphomas.[40,41] This also suggests being cautious about using new molecules until adequately powered studies have ruled out an excess risk of hematological malignancies, that are still associated with a substantial mortality rate.

Table 4 summarizes the current knowledge on the risks of excess cancers attributable to IBD drugs. Most of these cancers are hematological or skin cancers. Monotherapy with anti-TNF agents has been considered for 15 years as not associated with an excess risk of hematological malignancies.[42] However, in a French study using the nationwide medico-administrative data, a 2.5 multi-adjusted hazard ratio of lymphomas was reported in patients exposed to monotherapy with anti-TNF agents versus patients unexposed to anti-TNF agents or thiopurines.[43] This situation should be clarified in the near future by the results of the ongoing I-CARE cohort. The extent of clinical potential carcinogenesis associated with the use of vedolizumab and tofacitinib is unknown. Based on mechanistic concepts, it is important to specifically assess in the near future whether vedolizumab, which blocks the traffic of lymphocytes in the digestive tract, does not impair the immunosurveillance of digestive cancers. We also need to determine that tofacitinib, which promotes clinical reactivation of VZV infection, does not also induce EBV-related lymphomas. The gap of knowledge is less pronounced in the case of ustekinumab, since there is no safety signal regarding cancers in a psoriasis registry,[44] keeping in mind a different background disease, a limited power and lower doses of ustekinumab than those used in IBD.

Prevention, risk limitations and detection strategies

There is no specific prevention of IBD drug-induced hematological malignancies (Table 5). The only way to limit the incidence of these cancers is to limit the use of carcinogenetic drugs in

patients at highest risk, except in cases of severely active disease without therapeutic alternative associated with a similar expected efficacy. Given the high risk of EBV-related lymphoma[45] and urinary tract cancer[6] in men over the age of 65 years (not in women), avoidance of prolonged use of thiopurines can be considered in this context,[46] even if this suggestion does not yet appear in malignancy guidelines. Given the risk of postmononucleosis lymphoma, alternatives to a prolonged use if thiopurines can be considered in EBV-seronegative patients, particularly young men,[47] except when patients have severe uncontrolled IBD and no alternative to combination therapy. The risk of hepatosplenic T-cell lymphoma in young males with controlled IBD who are co-treated with thiopurines and anti-TNF agents can be reduced by limiting the duration of the combined treatment to 2 years.[47] Because IBD itself is suspected to promote skin cancers,[5] in addition to multiple genetic and nongenetic risk factors that are not IBD-related,[48] sun protection measures (https://www.who.int/uv/sun_protection/en) and regular full-body skin examinations should be recommended from diagnosis.[47] Intervals between skin examinations should be defined by a dermatologist,[47] on the basis of the patient's non IBD-related risk factors for skin cancer,[48] and the expected impact of the immunosuppressant drugs being used. In the future, the incidence of uterine cervix cancer will probably decrease if the HPV vaccine becomes widespread. In the meantime, women with IBD should adhere strictly to the universal screening programs according to country modalities. Whether women exposed to thiopurines require shorter surveillance intervals is not evidence-based. Again, intervals between screening examinations should be defined by the organ specialist (in this case, a gynecologist), taking into account all risk factors.

How to treat IBD in a patient with malignancy

Is there a latent malignancy when starting immunosuppressive therapy?

Immunosuppressive agents can cause de novo cancers but can also accelerate progression of latent cancers. Pretransplant screening in patients over the age of 50 years at significant risk of

sporadic cancers is part of the pretransplant evaluation in solid organ recipients.[49] Despite the lack of current guidelines, it could be suggested to review personal and family risk factors for cancers in older patients before starting any immunosuppressive therapy and consider performing screening exams according to individual contexts (such as chest-CT scans in heavy smokers) in addition to screening exams recommended in the general population.

Patients with cancer that has just been diagnosed

As a general rule, when patients are exposed to immunosuppressive therapy (immunomodulators [including tofacitinib] and biologics) at the time of cancer diagnosis, it is recommended that thiopurines, calcineurin inhibitors, and anti-TNF agents should be stopped, especially when IBD is in remission, at least until cancer therapy is completed.[50] But specific situations may lead to maintain the immunosuppressive therapy of IBD in agreement with the oncologist (Figure 1). This may be discussed for example in patients with refractory IBD that has been finally brought into remission by ustekinumab. This can also be considered in patients who are in deep remission under monotherapy with thiopurines and who develop a first instance of skin basal cell carcinoma at low risk of recurrence.[47] In these patients, treatment with thiopurines can also be prolonged, but generally stopped thereafter if a second skin cancer is diagnosed. It must be noted that corticosteroids are often included in chemotherapy protocols, which favors the maintenance of IBD remission. In cases of advanced cancer with no therapeutic curative perspective and severely active IBD, quality of life may be considered the priority and immunosuppressive therapy may be used (including anti-TNF agents[51] that do not obviously favor the growth of metastases[52]), if there is no therapeutic alternative.

When and how to resume immunosuppressive therapy after cancer cure?

In the general population, patients with previous cancer have a 14% increased risk of developing a new cancer compared with age and gender-matched controls.[53] This excess risk is maximal in adolescents, and is no longer apparent beyond the age of seventy years. This gradient is attributed to genetic susceptibility to cancers and late carcinogenic effects of treatment of the

first cancer (radiation therapy, chemotherapies) in younger patients. In cohorts of patients with IBD, this excess risk of new organ cancer has been confirmed in patients with past cancer, but without a strong impact after adjustment of resumption of immunosuppressive therapy.[54–56]

In clinical practice, the management priority is to avoid recurrence of the previous cancer that could be at least partly attributable to the resumption of immunosuppressive therapy. Indeed, cancer recurrence is often a death sentence. There is also a psychological dimension: if cancer recurrence occurs after the resumption of immunosuppressive therapy, both the gastroenterologist and the patient will suspect that the recurrence was favored by the resumption of the immunosuppressive treatment.

The impact of immunosuppressive therapy has been explored in rheumatology cohorts,[57,58] IBD cohorts,[54,55] and a recent meta-analysis.[56] None of these studies concludes a clear promoting effect of immunosuppressive therapy. Nevertheless, great caution is necessary in interpreting these results. First, in current clinical practice, the use of immune-suppressive therapy is avoided in patients with cancers at the highest risk of recurrence. This is a strong propensity bias: if the effect of immunosuppressive therapy is neutral, unadjusted cancer recurrence rates would be higher in patients who are unexposed to immunosuppressive therapy! Second, the fact that checkpoint inhibitors help patients who are cured from melanoma to stay recurrence-free[59] suggests that it is important to preserve cells responsible for immunosurveillance, especially in the early post-cancer period during which the immune system must clear residual tumor cells. The impact of various immunosuppressive drugs currently used in IBD on these cells is not known. Finally, we should take into account the experience of transplant specialists, at a time when thiopurines were the standard immunosuppressive regimen. In the 1990s, Penn reported an overall 21% post-transplant recurrence rate in patients with previous cancer.[60] High, intermediate and relatively low rates were observed when the time between cancer cure and initiation of thiopurines was below 2 years, between 2 to 5 years and more than 5 years, respectively. There were also substantial differences in the rate of recurrence according to the

type of organ cancer. Penn proposed to distinguish organ cancers according to which they are at high, intermediate or low risk of recurrence (Suppl Table 2).

Taking into account all these elements, it has been suggested in 2015 ECCO guidelines to try to implement a pause interval before starting or resuming immunosuppressive therapy, as follows:[47] 2-years for cancers with a low posttransplant recurrence rate and 5 years for cancers with intermediate or high post-transplant recurrence rate.

A management algorithm for patients with cured cancer is proposed in Figure 1. There are 3 points that differ from ECCO guidelines. First, we estimate that the pivot of the decision tree is the oncologist's estimation of the expected recurrence rate of the individual cancer. This estimation should not be based on old transplant publications, but should be a synthesis of cancer characteristics (histological and molecular subtype, stage) and prognostic data from updated oncology literature. Second, we suggest resuming immunosuppressive therapy at any moment in cases of uncontrolled IBD with no alternative with the same expected efficacy, as well as resuming immunosuppressive therapy as soon as necessary in patients with a very low risk of recurrence. We also suggest adapting the pause interval to the recurrence risk of the individual cancer (5 to 10%, or superior to 10%). Third, we suggest remaining cautious beyond 5 years in cancers with a risk of late recurrence, notably some breast cancers[61] and melanomas.[62]

Whenever immunosuppressive therapy is started or resumed, there are two golden rules in choosing an immunosuppressive drug: first, do not initiate or resume drug class with an established or suspected promoting effect on the index cancer (see Table 4 and Supplementary Table 3; for instance, anti-TNF agents are contra-indicated in a patient with previous melanoma); second, among drug classes with similar expected efficacy, give priority to drugs without any established or suspected carcinogenic effect (Table 4 and Supplementary Table 3).

Conclusion

Drug class-specific complications are usually identified early in the history of an IBD drug. Some thiopurine–associated complications can be predicted by genetic tests. Most other complications can be avoided by respecting contra-indications and biological drug monitoring measures that are recommended by drug agencies. Serious extraintestinal infections related to IBD and/or to IBD treatment are frequent in patients with IBD, and are associated with significant mortality in older patients. Their incidence can be reduced by vaccination strategies and detection/treatment of latent infections before starting immunosuppressive therapy. There is no preventive protocol for cancers attributable to IBD drugs. The incidence of thiopurine–related lymphomas can be limited by restricting the use of thiopurines in older men and in EBV-seronegative patients. Sun protection and skin surveillance are recommended from the time of diagnosis in all patients with IBD. In patients with previous cancer at substantial risk of recurrence, a pause in the use of immunosuppressive drugs is recommended, except in patients with severe disease without relevant therapeutic alternatives. In this context, physicians should favor the use of immunosuppressive therapy with no impact on the carcinogenesis of the index cancer, and with the lowest overall established or suspected oncogenic properties. The enumeration of the risks of IBD drugs should not mask the fact that the extensive use of immunosuppressive therapy leads to a substantial decrease in the incidence of IBD complications, with a globally favorable benefit-risk ratio, which can be further optimized thanks to a good degree of awareness and knowledge of drug complications.

Figure legends

Figure 1. How to treat IBD after a malignancy. Immunosuppressive therapy refers to biologics and old (thiopurines, methotrexate) and new (tofacitinib) immunosuppressive small molecules.

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Table 1. Prediction, prevention, detection and management of drug class-specific complications of IBD drugs (excluding corticosteroids)

Drug class	Complication	Prediction/ prevention	Detection	Management
Mesalazine[a]	Impaired renal function		Blood monitoring of renal function	Drug withdrawal Consider renal biopsy if the renal function does not recover to baseline
	Pneumonitis		Chest CT-scan	Pulmonary evaluation
	Cardiac events		Cardiology evaluation in case of chest symptoms	Drug withdrawal, in most cases definitive
Thiopurines	Myelosuppression	TPMT status NDT15 genotyping	Blood cell count monitoring according to the SMPC	Dose reduction or drug withdrawal according to severity
	Cholestasis and/or pancreatitis within the first two months of treatment		Liver test monitoring (cholestasis), serum lipase activity in case of unexplained abdominal pain	Drug withdrawal
	Liver nodular regenerative hyperplasia[b]		Platelet count and liver tests monitoring for detecting a progressive drop in the platelet count and cholestasis Imaging techniques when portal hypertension is suspected	Confirmation with elastometry/liver biopsy Definite drug withdrawal if confirmed
Methotrexate	Myelosuppression	Respect contraindicated drug combinations and dose adaptations according to the SMPC	Blood cell count monitoring according to the SMPC	Dose reduction or drug withdrawal according to severity
	Interstitial pneumonitis		Chest CT-scan and pulmonary evaluation in case of pulmonary symptoms, including unexplained cough	Definitive drug withdrawal if confirmed
	Liver injury		Liver tests monitoring according to SMPC instructions	Liver evaluation, including elastometry, in case of sustained elevated ALT
Anti-TNF agents[c]	Leucopenia and thrombopenia		Blood cell count at least every 6 months	Consider drug withdrwal according to severity
	Autoimmune-like disorders[d]		Evaluation according to alert clinical symptoms	Therapeutic approach according to the disease phenotype Consider drug withdrawal according to severity
	Demyelination	Respect absolute and relative contraindications of SMPC	Neurological imaging and evaluation according to symptoms	Definitive drug withdrawal if drug-induced demyelination is suspected
	Worsening cardiac failure	Respect contraindications of SMPC	Cardiologic evaluation in case of cardiac failure	Drug withdrawal in case of worsening of cardiac failure
	Disabling psoriasis		Dermatology evaluation	Drug withdrawal according to severity and the response to topic drugs

	Infusion reactions			Discontinuation of infusion in case of severe reactions Limited evidence for the use of premedication for preventing recurrence
Natalizumab[e]	Progressive multifocal leukoencephalopathy	Restricted and selective use of natalizumab in Crohn's disease	No predictive tool of developing progressive multifocal leukoencephalopathy	
Vedolizumab	None identified at the moment			
Ustekinumab	None identified at the moment			
Tofacitinib[f]	Pulmonary embolism	Do not use tofacitinib 10 mg bid in patients at high risk		
	Neutropenia, lymphopenia		Blood cell count according to the SMPC	Dose adaptation or drug withdrawal according to severity

IBD, inflammatory bowel disease; CT, computed tomography; TMPT, thiopurine-methyl-transferase; SMPC, summary of product characteristics; ALT, alanine aminotransferase; TNF, tumor necrosis factor
[a]Data are from Sehgal et al.[7]
[b]Patients at higher risk are men with previous extensive small bowel resection[63]
[c]Data are from Shivaji et al.[8]
[d]Include lupus-like syndrome, vasculitis, antiphospholipid syndrome, interstitial lung disease, optical neuritis, multiple sclerosis-like demyelination and peripheral neuropathies[64]
[e]Data are from Nelson SM et al.[65]
[f]Safety signal from patients with rheumatoid arthritis

Table 2. Elements to be taken into account from the diagnosis of IBD for adequately managing the risk of infections.[a]

	Topic
Infection history Record details of past and current infections, including chickenpox, genital herpes simplex, intertrigo, recurrent urinary or ear infections	Bacterial Fungal Viral
Risk factors for infection If any apply, consider and discuss the risks of opportunistic infection before starting or increasing immunosuppression	Country of origin/ethnicity (for tuberculosis) Contacts (especially tuberculosis) Residence in the tropics or endemic area Current immunosuppressive therapy[b] Treatment in the past for active or latent tuberculosis Elderly age Malnutrition Severe comorbidity
Immunization history For recording in hospital notes, usually available from general practitioner; if patient is not vaccinated, consider and discuss vaccination	Bacillus Calmette-Guérin (according to national practices) Hepatitis B Influenza Human papillomavirus Varicella zoster virus Diphtheria, tetanus and pertussis Pneumococcal vaccination
Future plans If the patient is taking immunomodulators or at risk of infection, consider and discuss infections endemic to countries to be visited. Advice from a specialist may be necessary	Travel to the tropics or endemic area
Physical examination Record height and weight, note areas often overlooked (e.g., fungal infections),	Nutritional status (body mass index) Signs of local or active infection Cervical smear if appropriate

IBD, inflammatory bowel disease

[a]A standardized checklist can be downloaded from the ECCO website (https://www.eccoibd.eu/publications/eccoguidelines-science/published-ecco-guidelines.html).

[b] the Immunosuppressive impact of IBD drugs is usually considered as high for systemic corticosteroids (more than 20 mg per day of prednisolone for more than 2 weeks, or more than 6 mg per day of budesonide), thiopurines and methotrexate at usual doses, anti-TNF agents and tofacitinib and low for other doses of corticosteroids (less than 20 mg daily of prednisolone or more than 20 mg of prednisolone for less than two weeks or budesonide dose inferior or equal to 6 mg per day), ustekinumab and vedolizumab

Table 3. Vaccination strategy in patients with IBD

	Item
General population vaccines	Follow a routine vaccination program including age-specific vaccines (i.e. influenza, zoster) according to country-specific guidelines Live vaccines are contra-indicated during immunosuppressive therapy[a]
On diagnosis of IBD	VZV vaccine (if no history of chickenpox and negative VZV serology, contra-indicated during immunosuppressive therapy) Hepatitis B (if hepatitis B virus serology is negative) Influenza (trivalent inactivated) Human papilloma virus
Prior to immunomodulators	Pneumococcal vaccines[a]
Annually	Influenza (trivalent, inactivated)
Booster	Pneumococcal polysaccharide vaccine (5 years)
Discretionary	Travel vaccines: take advice from appropriate specialist; live vaccines (e.g., yellow fever, oral poliomyelitis) are contra-indicated during immunosuppressive therapy

TNF: tumor necrosis factor; VZV: varicella zoster virus.
[a]Preferably start with the 13-valent conjugate vaccine, followed 2 months later by the 23-valent polysaccharide vaccine

Table 4. Current knowledge on cancers that can be promoted by IBD drugs

Risk	Drug class	Malignancy	Patients at risk	Absolute excess risk level
Established	Thiopurines	EBV-related posttransplant-like lymphomas[a]	All patients	Low to high in EBV-seropositive patients: age and gender-dependent (strongly increases with age, doubled in men); reversible after drug withdrawal High in EBV–seronegative patients[b]
		Hepatosplenic T-cell lymphoma[c]	Mainly young men exposed to combination of thiopurines and anti-TNF agents for more than 2 years	Very low
		Acute myeloid leukemia and myelodysplastic syndromes[d]	Previous exposure to thiopurines	Low
		Nonmelanoma skin cancers[e]	All patients	Low to high: increases with age and associated non-IBD related risk factors Conflicting data on the persistence of the excess risk after drug withdrawal[f]
		Urinary tract cancers[g]	Men over the age of 65 years	High in active smokers
	Anti-TNF agents	Melanoma[e]	All patients	Low
		Hepatosplenic T-cell lymphoma[c]	Mainly young men exposed to combination of thiopurines and anti-TNF agents for more than 2 years	Very low Not established in patients exposed to monotherapy with anti-TNF agents
Still uncertain	Anti-TNF agents	Lymphoma		Conflicting data[h]
	Methotrexate	Nonmelanoma skin cancers		Recently, reported in a randomized controlled trial of methotrexate in patients without IBD[i]
	Thiopurines	Uterine cervix cancer		Mild excess risk suggested in Danish population-based studies[j]
Unknown	Ustekinumab			
	Vedolizumab			
	Tofacitinib			

IBD, inflammatory bowel disease; EBV, Epstein-Barr virus
[a]Data are from Kotlyar et al.[45]
[b]Data are from Beaugerie et al.[40], and Hyams et al.[16]
[c]Data are from Kotlyar et al.[66]
[d]Data are from Lopez et al.[67]
[e]Data are from Long et al.[5]
[f]Data are from Peyrin-Biroulet et al.[68] and Abbas et al.[69]
[g]Data are from Bourrier et al.[6]
[h]Data are from Nyboe-Andersen et al.,[42] and Lemaitre et al.[43]
[i]Data are from Ridker et al.[70]
[j]Data are from Dugué et al.[71]

Table 5. Prevention, risk limitation and detection of cancers promoted by IBD drugs.

Cancer	Drug class	Prevention	Risk limitation	Screening/Detection
EBV-related lymphomas	Thiopurines		Consider avoiding the prolonged use of thiopurines in men over the age of 65 years,[a] except in severe IBD without therapeutic alternative	
Postmononucleosis lymphomas	Thiopurines		Consider avoid ingthe prolonged use of thiopurines in EBV-seronegative patients, particularly young men,[b] except in severe IBD without therapeutic alternative	
Hepatosplenic T-cell lymphoma	Combination of thiopurines and anti-TNF agents		Consider limiting the duration of combination therapy to two years in young men (below 35 years) with controlled IBD[b]	
Skin cancers	Thiopurines (nonmelanoma skin cancers) and anti-TNF agents (melanoma)	Sun protection[c]		Regular full-body skin examinations from the diagnosis of IBD[d]
Uterine cervix cancer	Thiopurines[e]	Vaccination against HPV[f]		Uterine cervix surveillance from the diagnosis of IBD[g]

IBD, inflammatory bowel disease; EBV, Epstein-Barr virus
[a]Data are from Dulai et al.[46]
[b]Data are from Annese et al.[47]
[c]Modalities can be found at https://www.who.int/uv/sun_protection/en
[d]Data are from Annese at al;[47] intervals between skin examinations should be defined by dermatologists
[e]The promoting role of thiopurines is still uncertain
[f]Data are from Rahier et al.[26]
[g]Modalities may differ among countries; intervals between screening examinations should be defined by gynecologists