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Balancing Benefit vs Risk of Immunosuppressive Therapy for Individual Patients With Inflammatory Bowel Diseases

Short title: Benefit-risk balance of immunosuppressive therapy in inflammatory bowel disease

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Abbreviations used in this paper:

CD, Crohn's disease

CESAME, Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France;

IBD, inflammatory bowel disease

JAK, Janus kinase

TNF, tumor necrosis factor

UC, ulcerative colitis

VTE, venous thromboembolism events

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ABSTRACT

Inflammatory bowel diseases (IBD) and their treatments, particularly immunosuppressive drugs, increase risk of infections and cancers. However, by promoting mucosal healing, these agents should reduce risks of infections related to intestinal lesions, malnutrition, intravenous devices, and IBD surgeries and reduce risk of cancers associated with chronic mucosal inflammation—although there are few data to support this concept. Corticosteroids increase the risk of vascular thromboembolic events, yet other immunosuppressive drugs that induce deep remission from IBD could decrease the incidence of cardiovascular events attributable to systemic inflammation and IBD-related hospitalizations and/or surgeries. The nature and magnitude of the risks of infections and cancers vary with immunosuppressive drug class and patient sex and age. For example, thiopurines increase risk of viral infections that might be fatal in young patients, whereas tumor necrosis factor antagonists increase risk of bacterial and intracellular infections that can be fatal in patients of any age, but particularly in older patients. The ability of drugs to prevent IBD-associated colorectal cancer varies with IBD location and duration. Models to assess the benefit:risk ratio of long-term use of immunosuppressive drugs for patients with IBD should be adapted based on patients' age, sex, and IBD phenotype, to properly guide patient management. The decision-making process should begin with a clear explanation of treatment risks and then integrate the patient's emotional perception of risks.

Key words: risk–benefit analysis, Crohn's disease, ulcerative colitis, emotional bias

Crohn's disease (CD) and ulcerative colitis (UC) are characterized by continuous or relapsing intestinal inflammation. Both inflammatory bowel diseases (IBDs) are lifetime diseases. Most of the treatments that are currently used are anti-inflammatory drugs. These anti-inflammatory drugs, except 5-amino-salicylates, also exhibit immunosuppressive properties.

Immunosuppressive drugs that are used for the treatment of IBD include small molecules (corticosteroids, thiopurines, and methotrexate) and biologics (anti-Tumor Necrosis Factor (TNF) agents, vedolizumab, and ustekinumab). New biologics and immunosuppressive small molecules (Janus kinase (JAK) inhibitors and Sphingosine 1 phosphate receptor modulators) are under development. Because of the possible complications of immunosuppression, clinicians do not consider using these drugs on a lifetime basis. There is a growing trend towards a cyclic use of these drugs. When making the decision to enter a therapeutic cycle, clinicians and patients are interested in benefit-risk balance modeling studies, which should ideally integrate all benefits and risks associated with therapeutic strategies. This research area is recent in IBD. Major advances occurred within the last years because of growing access to medico-administrative databases and initiation of well-phenotyped observational cohorts.

Potential impact of immunosuppressive therapy on morbidity and mortality in IBD

In westernized countries, the two primary causes of death are cardiovascular disease and cancer.¹ This is also true for individuals living with IBD.² In developed countries, death by infection (mainly influenza and pneumonia) is twenty times less frequent than death by cancer.³

Patients with IBD may develop cancers, cardiovascular events and infections that are not related to IBD or IBD treatment, are attributable to IBD itself, or are attributable to IBD treatment. Immunosuppressive drugs have been shown to promote immunosuppression-related infections and cancers (Figure 1). Via mucosal healing, immunosuppressants are also candidates for reducing the incidence of infections related to IBD. Finally, with the exception of corticosteroids that increase the risk of vascular thromboembolic events, it is plausible that immunosuppressive

drugs that lead to IBD deep remission could decrease the incidence of cardiovascular events attributable to IBD.

Expression of the magnitude of risks attributable to IBD or IBD drugs

The association between treatment exposure and outcomes of interest may be expressed in relative terms, such as relative risks or odds ratios. The absolute risk is the probability of the occurrence of a specified outcome within a period of time (incidence rate). Incidence rates are generally expressed as the number of events per patient-years. The denominator of 1000 persons-years is increasingly used in the IBD literature. The number of events per 1000 years represents the risk percentage of developing the event for a 10-year period.

For physicians, absolute and relative risks are complementary approaches for the integration of medical knowledge. In contrast, when considering an individual patient in clinical practice, absolute risks are exclusively relevant for determining the individual benefit-risk balance of a therapeutic strategy.

Figure 2 plots the magnitudes of the risks of key events that may be observed in individuals with IBD on a logarithmic scale. For each event category, numbers are the sum of events not related to IBD or IBD treatment, related to IBD, or related to IBD treatment. The qualifying adjectives that appear in the figure are those used by drug agencies for stratifying the magnitude of risks of adverse events associated with the use of new drugs.⁴

Data sources for assessing the magnitude of risks associated with IBD or IBD treatment.

The incidence of frequent events in IBD may be adequately estimated in reports from IBD centers or meta-analyses of randomized controlled trials. To estimate the risks of rare events, such as opportunistic infections or cancers, the minimum time of observation needed often exceeds 30,000 patient-years. This power may be attained in studies from medico-administrative databases or observational cohorts. Subgroup assessment of the risks according to age-class

and gender is possible in all studies. However, differential assessment of risks according to IBD phenotype is not possible in studies from most of the medico-administrative databases because data on IBD phenotype are lacking. To fill in this gap, data on IBD phenotype are recorded in dedicated prospective observational cohorts, such as CESAME or I-CARE ((Ibd CAncer and seRious infections in Europe, <https://clinicaltrials.gov/ct2/show/NCT02377258>).

Infections

Infections are extremely frequent in everyday life and can be categorized according to their clinical impact (Table 1). Serious infections are generally defined as infections that require hospitalization and may be life-threatening or result in permanent disability. In the IBD population, the incidence of serious infections ranges from 10 to 100 events per 1000 patient-years according study designs and care pathway specificities.⁵⁻⁷

Opportunistic infections occur selectively or are particularly severe in immune-compromised patients, and these infections are life-threatening. There is no universal list of opportunistic infections, and infections considered in the analyses vary among studies.^{6,8}

Notably, the same infectious agent, for example zoster, may cause benign, serious or opportunistic infections according to host and context specificities and disease severity.

Infections promoted by immunosuppressive therapy

The excess risk of infection in patients with IBD exposed to corticosteroids, thiopurines and anti-TNF varies among types of infection and drug classes (Table 2). Few data exist on everyday benign infections. It was reported in a prospective cohort of outpatients with IBD that exposure to thiopurines was associated with an increased incidence of skin herpes flares and skin viral warts.⁹ The incidence of zoster is intrinsically increased in patients with IBD.¹⁰⁻¹² Exposure to corticosteroids, thiopurines, and/or anti-TNF agents further increases this risk.¹⁰⁻¹²

A similar excess risk of serious infections in patients exposed to monotherapies with thiopurines

and anti-TNF agents was reported in a meta-analysis of randomized controlled trials.¹³ The excess risk primarily relates to viral infections in patients exposed to monotherapy with thiopurines.⁵ The risk of serious infections is even higher in patients exposed to corticosteroids or combination therapy with thiopurines and anti-TNF agents.^{5,14} There is an excess risk of opportunistic infections in patients exposed to monotherapies with thiopurines and anti-TNF agents.^{5,6,8,13,15,16} This risk is significantly higher in patients exposed to corticosteroids^{7,14,17} or combination therapy with thiopurines and anti-TNF agents.⁵

There is an excess risk of all types of infections in patients exposed to corticosteroids and/or anti-TNF agents, particularly older patients.^{17,18} In contrast, the excess risk primarily relates to viral infections in patients exposed to thiopurines.⁵ There is no excess mortality from infection at the population level in IBD patients exposed to thiopurines and anti-TNF agents,^{7,17,19} but some studies have reported an excess mortality from infection in patients exposed to corticosteroids.^{7,14,17} At an individual level, thiopurine-associated fatal infections have been reported mainly in young patients. These infections include severe forms of varicella²⁰ and primary Epstein-Barr virus or cytomegalovirus infections complicated with hemophagocytic lymphohistiocytosis.²¹ In patients exposed to anti-TNF agents, fatal cases of infections are related to various types of opportunistic infections,¹⁶. There are no data on the risk of infection in patients exposed to monotherapy with methotrexate in IBD. The first safety reports on vedolizumab in patients with IBD do not suggest an increased risk of serious infections.²² Data on infections in patients with IBD exposed to ustekinumab are lacking. However, no evidence of excess infections in patients receiving ustekinumab for psoriasis was reported.²³ Patients exposed to JAK inhibitors for UC are at substantial increased risk of herpes zoster, giving sense to vaccination strategies.²⁴

Impact of immunosuppressive therapy on IBD-related infections

In controlled trials, patients exposed to immunosuppressive drugs who achieve mucosal healing should be at reduced risk of infections related to intestinal lesions compared to patients with uncontrolled disease. Patients exposed to thiopurines and/or anti-TNF exhibit an increased risk of immunosuppressive drug-related infections. These counterbalancing effects result in an overall similar incidence of infections in patients exposed to placebo and anti-TNF agents and/or thiopurines.^{13,25}

Cancers

Cancers promoted by immunosuppressive therapy

The excess risk of cancer in patients with IBD exposed to corticosteroids, thiopurines and anti-TNF agents varies among organs and drug classes (Table 3). Patients with IBD exposed to thiopurines exhibit a mild overall excess risk of cancers.²⁶ All patients with IBD treated with thiopurines are at increased risk of EBV-associated lymphoma.²⁷ Young patients, particularly males, are at risk of post-mononucleosis lymphomas and hepatosplenic T-cell lymphomas.^{28,29} IBD patients exposed to thiopurines exhibit an increased risk of non-melanocytic skin cancers,^{30,31} and patients exposed to anti-TNF agents are at increased risk of melanoma.³⁰ Older men with IBD exposed to thiopurines are at increased risk of urinary tract cancers.^{26,32} Whether patients treated with anti-TNF agents alone exhibit an excess risk of lymphoma remains controversial.^{33,34} Patients treated with methotrexate for diseases other than IBD may develop reversible EBV-related lymphomas.³⁵ Safety data from patients treated with vedolizumab and ustekinumab in IBD are not yet powered to address the risks of cancer associated with the long-term drug exposure.

Chemopreventive effect of immunosuppressive therapy on cancers

Patients with IBD may specifically develop cancers in segments of the digestive tract that are chronically inflamed.²⁸ Subgroup analyses studies revealed no increased risk of colorectal

cancer,³⁶ small bowel adenocarcinoma,³⁷ anal canal cancer,³⁸ and cholangiocarcinoma,³⁹ in patients with IBD compared to age- and gender-matched individuals in the general population when the digestive organs are not chronically inflamed. In contrast, a marked increase in the risk of digestive tract cancers is observed when digestive organs are chronically inflamed.^{36–39}

Among immunosuppressive drugs used in IBD, thiopurines and methotrexate have been used in oncology as cytotoxic drugs, but these drugs have not exhibited effects on carcinogenesis itself. However, all immunosuppressive drugs used in IBD can reduce inflammation in intestinal segments that are affected by IBD, which could reduce in turn the risk of inflammation-related cancers. A chemopreventive effect of thiopurines in the risk of colorectal cancer in patients with UC has been reported in two nationwide cohorts. In the CESAME cohort, the adjusted hazard ratio for colorectal high-grade dysplasia or cancer among patients with longstanding extensive colitis was 0.28 for those who received thiopurines.³⁶ In the ENEIDA cohort, the use of thiopurines was associated with a decreased risk of colorectal advanced neoplasia by multivariate analysis.⁴⁰ No data from adequately powered cohorts are available for anti-TNF, vedolizumab or ustekinumab in this context.

Cardiovascular events

The increased risk of venous thromboembolism (VTE) is established in patients with IBD. Deep vein thrombosis and pulmonary embolism are the most common types of VTE. Population-based cohorts revealed a 1.5- to 3-fold higher risk for the development of VTE in patients with IBD compared to non-IBD controls.⁴¹ The highest risks are reported in patients with IBD flare, outside the hospital and without thromboprophylaxis.⁴²

Patients with IBD exposed to systemic corticosteroids exhibit an increased risk of VTE.^{43,44} A recent meta-analysis of the few existing studies assessed the impact of anti-TNF agents compared to corticosteroids on the risk of VTE. It was reported in this meta-analysis a 70%

decrease in the risk of VTE in patients with IBD treated with anti-TNF agents compared with those treated with corticosteroids.⁴⁴

Acute arterial events include ischemic heart disease, cerebrovascular disease and peripheral artery disease. In population-based studies of patients with IBD, the incidence rate of acute arterial events range from five to ten events per 1000 patient-years.^{45,46} A recent nationwide study reported an increased risk of acute arterial events in CD and UC compared to the general population.⁴⁶ The excess risk was higher in CD than UC, and the highest excess risks were observed in younger patients in both IBD subtypes. Clinical disease activity of IBD is associated with an increased risk of acute arterial events in both IBD subtypes after adjustment for all traditional cardiovascular risk factors. The risk increased by 1.5- to 2-fold during periods of active disease.^{45,46} The differences observed in subgroup analyses may be due to various respective impacts of systemic inflammation and traditional cardiovascular risk factors.^{46,47}

It is established that exposure to corticosteroids is associated with an increased risk of acute arterial events in IBD^{14,48} By contrast, it has been hypothesized that other immunosuppressive drugs that are used in chronic inflammatory diseases could decrease the incidence of acute arterial events. This has been demonstrated for myocardial infarction in patients exposed to methotrexate or anti-TNF agents in rheumatology.⁴⁹ Data from the French national medico-administrative database also suggest a significant reduction in the incidence of acute arterial events in patients with IBD exposed to combination therapy with anti-TNF agents and thiopurines.⁵⁰

Assessment of the benefit-risk balance of immunosuppressive therapy in IBD

Merging all of the findings on the benefits and risks of IBD immunosuppressive therapy is difficult for clinicians. Treatment benefits are reported in randomized controlled trials, and treatment risks or indirect treatment benefits (e.g., chemoprevention, cardiovascular protection) are reported in observational studies. One unique tool is adapted to combine all findings and aid clinical

decision-making. Clinical decision models were developed initially in the field of cost-effectiveness analyses.⁵¹ State-transition models,⁵¹ including the Markov model,⁵² are the most commonly used models in the field of IBD.^{53–55}

Time-scale to assess the benefit-risk balance of immunosuppressive therapy

The time-scale over which outcomes are assessed is the time horizon.⁵¹ Guidelines recommend a time horizon that is sufficiently long to capture differences in outcomes across treatment strategies.⁵¹ Since IBDs are lifetime diseases, the time horizon may be a lifetime. However, the time horizon that may be considered clinically relevant in IBD is the period of drug exposure because treatment-related benefits and risks generally do not persist after drug withdrawal. The concept of treatment cycle is emerging in the field of IBD,⁵⁶ but there is no clear cut-off for the duration of one treatment cycle. A time horizon of 5 years may be relevant to assess most treatment strategies, but the relevant duration may vary in specific situations, such as induction therapies (short-term assessment) or surgical strategies (long-term assessment).

Outcomes of interest

The highest priority in the overall management of individuals with IBD is to avoid death due to IBD or IBD drugs. Therefore, the primary health outcome is life expectancy. However, events that are not at risk of death are not considered in this model, but some events, such as permanent stomas, highly affect patients' lives.

Alternatively, quality of life may be used as the health outcome. The 'utility' associated with health states was introduced to estimate gains in Quality-Adjusted Life Years (QALYs).⁵⁷ In the field of inflammatory bowel disease, estimates of utility that are currently available are sparse and heterogeneous.⁵⁸

Key parameters to be included in the benefit-risk assessment

Personalized information on all risks and benefit parameters should become the standard of quality for guiding individual decision-making processes of treatment strategy. The historical evolution of decision models to assess the risk of lymphoma in patients with IBD exposed to thiopurines may illustrate this point. One of the first decision models published assessed the impact of thiopurines in patients with CD who achieved remission with corticosteroids.⁵³ This study provided subgroups analyses according to age only. Another study modeled the impact of the combination of infliximab with azathioprine compared to infliximab alone, and the risk of lymphoma was estimated according to age and gender.⁵⁴ Finally, in a recent study modeling the benefit-risk balance of continuing or withdrawing thiopurines in CD, the beneficial effect of thiopurines on colorectal cancer in the subgroup of patients with longstanding extensive colitis was also considered, with a substantial impact on results (Figure 3).⁵⁵ Future studies should increasingly provide subgroup analyses based on age, gender, and IBD phenotype to improve the precision of estimates from medical decision-making models in IBD.

Special situations that deserve specific assessments of the benefit-risk balance of immunosuppressive therapy

Patients over the age of 65 years have the highest risks of morbidity and mortality due to uncontrolled IBD, such as VTE⁵⁹ or perioperative death in UC.⁶⁰ Older patients are also at maximal risk of cancers attributable to thiopurines,²⁷ and serious and opportunistic infections due to corticosteroids, thiopurines and anti-TNF agents.^{5,18} In this context, the use of new biologics (vedolizumab and ustekinumab) and small molecules (JAK inhibitors) is attractive as long as no significant risk of cancer or death by infection has been demonstrated in the early development of these drugs. However, prudence is still required because older patients are usually not enrolled in randomized controlled trials and meta-analyses.

Additional elements must be taken into account in older patients.⁶¹ Priority could be given to reduce disabling digestive symptoms in patients often suffering from other disabling

comorbidities. In addition, treat-to-target and endoscopic surveillance strategies that aim to reduce the incidence of long-term complications of disease complications are often less crucial in patients with limited life-expectancy, due to age and comorbidities, particularly in patient with late-onset disease.

Pregnancy is another specific context. It is generally recommended that an active treatment should be maintained throughout pregnancy in women with chronic uncontrolled, or partially controlled, disease.^{62,63} Regarding the choice of drugs, it is established that thalidomide and methotrexate are contra-indicated because of their teratogenic effects. The use of corticosteroids, thiopurines and anti-TNF agents is considered at low risk during pregnancy, while the safety of vedolizumab, ustekinumab and JAK inhibitors is not established, due to a lack of data.

In patients with previous cancer, it is questionable whether continuation or resumption of immunosuppressive therapy could promote cancer recurrence. No obvious excess risk of cancer recurrence has been reported in patients with chronic immune disease exposed to immunosuppressive therapy,⁶⁴ although significant propensity biases cannot be excluded.⁶⁵ Based mainly on a precautionary principle, it is recommended to try to respect a 2 to 5-year pause in immunosuppressive therapy, according to the intrinsic risk of cancer recurrence, in patients with IBD after completion of cancer treatment.²⁹ However, in patients with severely active uncontrolled IBD, life-threatening risks of uncontrolled IBD are superior to putative risks of cancer recurrence.

Decision-making process

Communication on risks

When two or more alternative therapeutic strategies may be considered in a given individual with IBD, the first step of the shared decision-making process is to explain the risks of IBD and IBD drugs to patients. Some general recommendations have been proposed⁶⁶ based on the results

of dedicated surveys. Descriptive words (rare, very rare) should be avoided because absolute numbers associated with these adjectives vary considerably among individuals. Relative risks are difficult to conceptualize. When absolute risks are expressed as numbers, consistent denominators (e.g., number of events per 1000 person-years, see above) should be preferred. Finally, visual depiction of risks, such as the 'thousand people shapes', should be used as often as possible.

Communication on benefits

An equilibrated communication on the benefit-risk balance of different strategies should include equal parts of information on the risks of IBD drugs and the risks of uncontrolled IBD that may be attenuated or suppressed by the use of IBD drugs (Figure 1).⁶⁷

Decision-making process and emotional component

The magnitude of treatment risks that patients with IBD are willing to accept for a better control of IBD and an improved quality of life is a personal and subjective choice. Previous studies demonstrated that children with IBD and their parents and adults with IBD and gastroenterologists generally accept relatively high levels of risks of IBD drugs when IBD is severe.^{68,69} Individual emotional and personality factors may modulate or reverse final individual patient decisions. The therapeutic alternative that is associated with the best quality of life-adjusted life expectancy may be rejected because of irrational or emotional individual perception. For example, many individuals prefer to travel by car over traveling by plane despite the fact that the objective risk of dying in ground transportation is much higher. Psychosocial sciences have also demonstrated that individuals are more prone to accept long-term risks than short-term risks of the same magnitude. Gastroenterologists should be aware of the major role of patient emotions and personality and try to integrate these factors when talking about the benefits and risks of therapies with their patients.

Conclusion

In patients with severely active IBD, potential complications of IBD generally outweigh the potential complications of IBD drugs on a short-term basis, which results in a favorable benefit-risk balance of most IBD drugs. In contrast, in patients with sustained deep remission thanks to immunosuppressive therapy, the long-term cumulative risks of IBD drugs may outweigh the risks associated with disease relapse. Long-term risks of immunosuppressive drugs are strongly age- and gender-dependent. For example, drug-induced serious infections and thiopurine-associated lymphomas are at the highest frequency in older patients.^{5,18} Regarding gender, the standardized incidence ratio of lymphoma in men exposed to thiopurines is approximately twice the standardized incidence ratio in women exposed to thiopurines.²⁷ As a consequence, safety data that foster benefit-risk individual discussions should be tailored to age classes and gender. Intestinal cancers complicating IBD inflammation may be at least partially prevented with a sustained mucosal healing of intestinal lesions, and the magnitude of this potential benefit of IBD drugs should be progressively quantified in the near future. Moving progressively towards a personalized assessment of the benefit-risk balance of immunosuppressive IBD drugs is a prerequisite for a high-quality shared decision-making process on individual therapeutic strategies in patients with IBD.

Figure legends

Figure 1. Primary complications of immunosuppressive therapy used in inflammatory bowel disease (deleterious impact) and potential reduction in the incidence of complications of inflammatory bowel disease due to the anti-inflammatory effect of immunosuppressive therapy (beneficial impact).

Figure 2. Magnitude of the risks of infections, cancers and vascular events in the population of patients with inflammatory bowel disease. Numbers of events per 1000 patient-years are plotted using a logarithmic scale. For each event category, numbers are the sum of events not related to IBD or IBD treatment, related to IBD, or related to IBD treatment. Adjectives that qualify risk levels are used by drug agencies.

Figure 3. Lifetime absolute risks of lymphoma and colorectal cancer associated with continuing (C) or withdrawing (W) maintenance therapy with thiopurines in patients with CD in sustained clinical remission, according to age, gender and colonic extent (more or less than 50% of the mucosal surface ever involved) at the time of the decision. Adapted from Kirchgesner et al.⁵⁵

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Table 1. Classification of infections that may occur in patients with inflammatory bowel disease

Type	Definition	Impact
Benign infections (e.g., cold, oral herpes flare)	Are not life-threatening Do not require hospitalization	If repeated, may impair quality of life
Serious infections (e.g., intra-abdominal abscess, severe pneumonitis)	Require hospitalization and/or result in permanent disability	May be life-threatening
Opportunistic infections (e.g., aspergillosis, severe forms of varicella)	Occur selectively or are particularly severe in immunocompromised patients	Are life-threatening

Table 2. Excess risk of infection and infection-related mortality in patients with inflammatory bowel disease exposed to corticosteroids, thiopurines and anti-Tumor Necrosis Factor (TNF) agents compared to patients not exposed to immunosuppressive drugs.

	Incidence rate (cases per 1000 person-years) in total IBD population	Adjusted hazard ratio (HR (95% CI) in patients with IBD exposed to immunosuppressive therapy versus those not exposed to immunosuppressive therapy		
		Thiopurines alone	Anti-TNF agents alone	Thiopurines in combination with anti- TNF agents
Benign infections Overall	ND	ND	ND	ND
Zoster ^a	7.6	HR: 1.5 (1.3-3.7)	HR: 1.2 (0.9-1.4)	HR: 1.7 (1.2-2.2)
Serious infections	9.8 ^b	HR: 1.3 (1.2-1.4) ^b	HR: 1.6 (1.0-2.6) ^c	HR: 2.8 (2.4-3.2) ^b
Opportunistic infections Overall ^b	0,8	HR: 3.7 (3.0-4.6)	HR: 4.0 (3.1-5.3)	HR: 7.9 (5.40-11.4)
Viral ^b	0,3	HR: 9.0 (6.6-12.3)	HR: 5.2 (3.2-8.3)	HR: 10.2 (5.5-19.0)
Bacterial ^b	0,2	HR: 1.9 (1.1-3.3)	HR: 4.5 (2.7-7.4)	HR: 9.0 (4.5-18)
Fungal	0.2 ^d	HR: 1.5 (0.7-3.6) ^b	HR: 1.9 (0.8-4.8) ^b	HR: 1.5 (0.4-5.7) ^b
Infection-related mortality	0.4 ^b	ND	ND	ND

CI, confidence interval; ND, no data

^a Data are from Khan et al.¹²

^b Data are from Kirchgessner et al.⁵

^c Data are from Nyboe-Andersen et al.⁶

^d Data are from Lichstentein et al.¹⁷

Table 3. Absolute risk of cancer in patients with inflammatory bowel disease (IBD), and adjusted ratio of cancer in patients with IBD exposed to thiopurines and/or anti-Tumor Necrosis Factor (TNF) agents, compared to patients not exposed to immunosuppressive drugs.

	Incidence rate (cases per 1000 person-years) in total IBD population	Adjusted rate ratio (RR (95% CI)), hazard ratio (HR (95% CI) or odds ratio (OR (95% CI) in patients with IBD exposed to immunosuppressive therapy versus those not exposed to immunosuppressive therapy		
		Thiopurines alone	Anti-TNF agents alone	Thiopurines in combination with anti-TNF agents
All cancers, excluding non-melanocytic skin cancers	7.3 ^a	RR:1.4 (1.2 – 1.7) ^b	RR: 1.1 (0.9-1.4) ^a	ND
Hematological malignancies				
All	0.5 ^a	ND	RR: 0.9 (0.4-1.9) ^a	ND
Lymphoma ^b	0.3 ^c	HR: 2.6 (2.0-3.4) ^c	HR: 2.4 (1.6-3.6) ^c	HR: 6.1 (1.3-4.2) ^c
Skin cancers				
Non melanocytic skin cancer	9.1 ^d	OR: 1.9 (1.7-2.1) ^d	OR: 1.1 (0.9-1.4) ^d	ND
Melanoma	0.4 ^a	OR: 1.1 (0.7-1.7) ^d	OR: 1.9 (1.1-3.3) ^d	ND
Urinary tract cancer ^e	0.3 ^a	HR: 2.8 (1.0-7.7) ^e	RR: 1.6 (0.6-4.2) ^a	ND

CI, confidence interval; ND, no data

^a Data are from Nyboe-Andersen et al.³³

^b Data are from Pasternak et al.²⁶

^c Data are from Lemaitre et al.³⁴

^d Data are from Long et al.³⁰

^e Data are from Bourrier et al.³²

Immune-suppressive therapy in IBD may:

Decrease (benefit)

Provoke (risk)

Provoke (risk)

	<i>Complications of IBD</i>	<i>Complications of immunosuppression</i>	<i>Drug-class specific complications</i>
<i>Infections</i>	Related to <ul style="list-style-type: none">• intestinal lesions (abscesses)• intravenous devices• malnutrition• surgery for IBD	Related to immunosuppression <ul style="list-style-type: none">• various infections (including opportunistic infections)	<ul style="list-style-type: none">• Bone marrow suppression (thiopurines)• Interstitial pneumonitis (methotrexate)• Leuko-encephalopathy (anti-TNF)
<i>Cancers</i>	Related to chronic inflammation <ul style="list-style-type: none">• colorectal cancer• small bowel adenocarcinoma• anal cancer	Related to immunosuppression <ul style="list-style-type: none">• mainly lymphomas and skin cancers	
<i>Cardio-vascular events</i>	Related to inflammation, hospitalization, or surgery for IBD <ul style="list-style-type: none">• venous thromboembolic events• acute arterial events