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# Accepted Manuscript


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Julien Kirchgesner, Magali Lemaitre, Fabrice Carrat, Mahmoud Zureik, MD; Franck Carbonnel, Rosemary Dray-Spira

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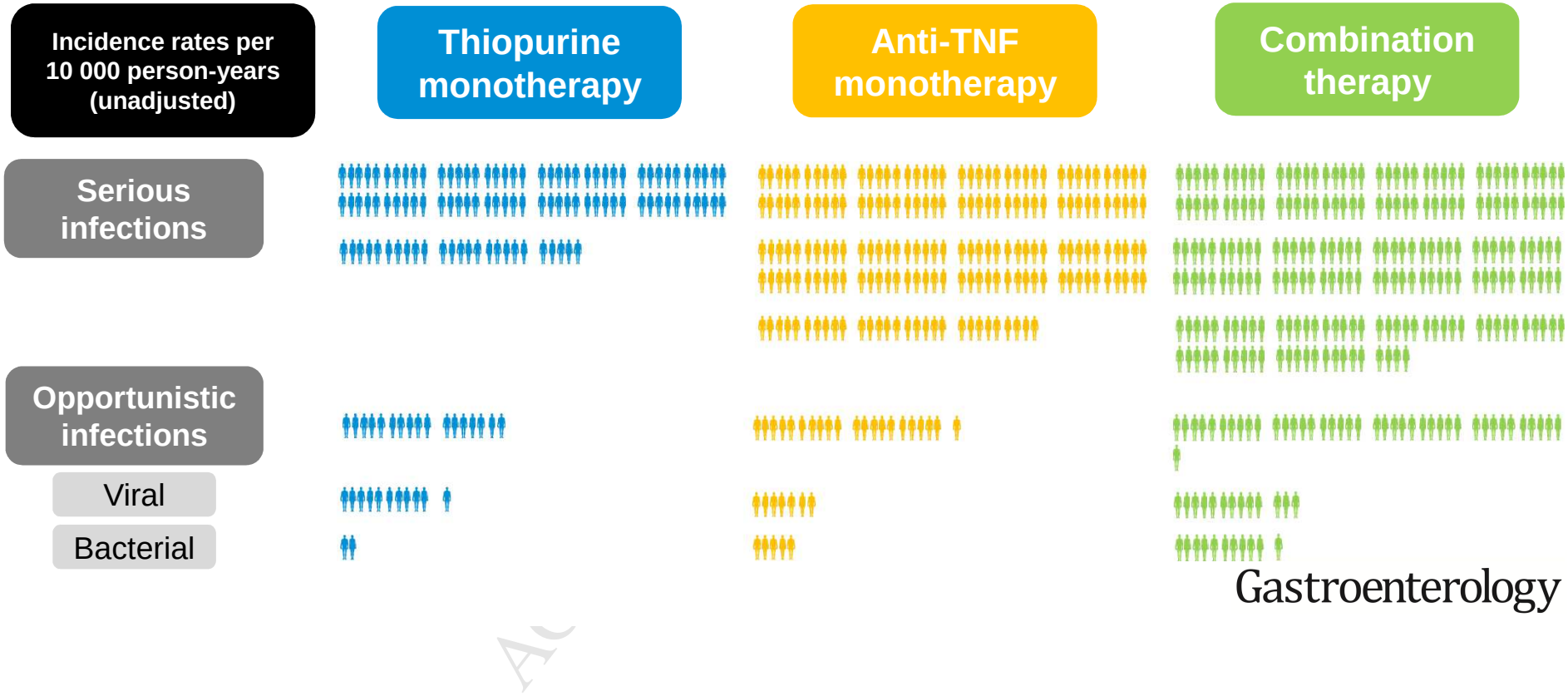

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# Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases

Julien Kirchgesner[1,2,3], Magali Lemaitre[1], Fabrice Carrat[2], Mahmoud Zureik[1], MD; Franck Carbonnel[4], Rosemary Dray-Spira[1]

(1) Department of Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety, Saint-Denis, France

(2) UMR-S 1136, INSERM & UPMC Univ Paris 06, Paris, France

(3) Department of Gastroenterology, AP-HP, Hôpital Saint-Antoine, Paris, France

(4) Department of Gastroenterology, AP-HP, Hôpitaux Universitaires Paris Sud, Le Kremlin Bicêtre, France

Short title: Infections in IBD

Corresponding author: Rosemary Dray-Spira

Health Product Epidemiology Department, French National Agency for Medicines and Health Products Safety (ANSM)

143-147 boulevard Anatole France

F-93285 Saint-Denis cedex, France

E-mail: Rosemary.DRAY-SPIRA@ansm.sante.fr

Tel: +33 (0)1 55 87 38 23

Fax: +33 (0)1 55 87 35 22



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Author contributions:

Study concept and design: All authors. Acquisition of data: Julien Kirchgesner. Analysis of data: Julien Kirchgesner, Magali Lemaitre and Rosemary Dray-Spira. Statistical analysis: Julien Kirchgesner and Rosemary Dray-Spira. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit this manuscript for publication. All the authors had access to the study data and had reviewed and approved the final manuscript.

Conflict of interest:

Franck Carbonnel has received consulting fees from Genentech, Otsuka and Vifor and lecture fees from Hospira. Fabrice Carrat has received consulting fees from Imaxio. Julien Kirchgesner, Magali Lemaitre, Mahmoud Zureik and Rosemary Dray-Spira disclose no conflicts

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Abbreviations used in this paper: IBD: Inflammatory bowel disease; SNIIRAM: Système National d'Information Inter-Régimes de l'Assurance Maladie; LTD: long-term diseases; ICD-10: International Classification of Diseases, 10th edition; anti-TNFs: anti-tumor necrosis factor agents.



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**Abstract:**

Background & Aims: The risk of infection associated with tumor necrosis factor antagonists (anti-TNF) and thiopurines (combination therapy) is uncertain. We assessed the risk of serious and opportunistic infections in patients with IBD treated with thiopurine monotherapy, anti-TNF monotherapy, or combination therapy in a large cohort of patients in France.

Methods: We performed a nationwide population-based study of patients (18 years or older) with a diagnosis of IBD in the French national health insurance database; we collected data from January 1, 2009 until December 31, 2014. The risks of serious and opportunistic infections associated with exposure to combination therapy, anti-TNF, and thiopurine monotherapies were compared using marginal structural Cox proportional hazard models adjusted for baseline and time-varying socio-demographic characteristics, medications, and comorbidities.

Results: Among the 190,694 patients with IBD included in our analysis, 8561 serious infections and 674 opportunistic infections occurred. Compared to anti-TNF monotherapy, combination therapy was associated with increased risks of serious infection (hazard ratio [HR], 1.23; 95% CI, 1.05–1.45) and opportunistic infection (HR, 1.96; 95% CI, 1.32–2.91). Compared with thiopurine monotherapy, anti-TNF monotherapy was associated with increased risks of serious infection (HR, 1.71; 95% CI, 1.56–1.88), mycobacterial infection (HR, 1.98; 95% CI, 1.15–3.40) and bacterial infection (HR, 2.38; 95% CI, 1.23–4.58, respectively). Conversely, anti-TNF monotherapy was associated with decreased risk of opportunistic viral infection compared to thiopurine monotherapy (HR, 0.57, 95% CI, 0.38–0.87).



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Conclusions: In a nationwide cohort study of patients with IBD in France, we found heterogeneity in risks of serious and opportunistic infections in patients treated with immune-suppressive regimens. These should be carefully considered and weighed against potential benefits for IBD treatment in patient management.

Keywords: inflammatory bowel disease; thiopurines; anti-TNFs; combination therapy.

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## Introduction

The combination of tumor necrosis factor antagonists (anti-TNF) and thiopurines (combination therapy) is more effective than monotherapy with either of these drugs in patients with Crohn's disease and ulcerative colitis.[1,2] This association is increasingly recommended in patients with inflammatory bowel disease (IBD).[3,4] However, the use of thiopurines and anti-TNFs is associated with adverse effects, notably infections and malignancies.[5,6] Several studies have shown an increased risk of serious and opportunistic infections in patients treated with anti-TNFs or thiopurines as monotherapy for IBD.[7–10] It is unclear if this risk is higher with anti-TNFs than with thiopurines, and if combination therapy carries a higher risk than monotherapy. Meta-analyses and pooled analyses of randomized controlled trials do not suggest an increased risk of serious infections with combination therapy,[11–13] while an increased risk of opportunistic infections has been reported compared to anti-TNF monotherapy.[14] Differences in site and pathogen specific infections may explain the inconsistency of previous findings. Most importantly, these results are based on limited samples of selected patients. They may lack sufficient power to detect risk differences and may not apply to the general population of unselected patients. Therefore, large population-based studies are needed to better define the benefit-risk balance of these drugs.

The aim of this population-based study was to compare the risks of serious and opportunistic infections between thiopurine monotherapy, anti-TNF monotherapy, and combination therapy in a large sample of patients with IBD.



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# Methods

## Data sources

This cohort study was based on the French National Health Insurance database (Système National d'Information Inter-Régimes de l'Assurance Maladie, SNIIRAM),[15] which covers 95% of the French population with different insurance schemes based on employment situation. The general health insurance scheme covers employees in the industry, business and service sectors, public service employees and students, accounting for approximately 88% of the French population. Due to data availability and quality, only individuals insured by the general scheme were considered. Excluded insurance schemes cover specific professions and do not depend on comorbidities or medical conditions.

The SNIIRAM provides individual data on all drug reimbursements and outpatient medical care prescribed by healthcare professionals as well as individuals' status with respect to full reimbursement of care for severe long-term diseases (LTD),[15] including Crohn's disease and ulcerative colitis. Using a unique anonymous identifier, information from the SNIIRAM is linked to the French national hospital discharge database which provides individual medical information since 2006 on all hospital admissions in France, including discharge diagnoses (International Classification of Diseases, 10th edition [ICD-10]) and medical procedures performed. These databases have been used previously for large pharmacoepidemiological studies.[16–20]

This study was approved by the French Data Protection Authority. All data used in this study only contained anonymous patient records.



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## Study population

The source population included all patients aged 18 years or older identified with IBD before 2014 from the French administrative health databases. Identification of IBD cases was based upon LTDs and/or hospitalization discharges including ICD-10 codes of Crohn's disease or ulcerative colitis. Patients with a single hospital discharge diagnosis of IBD and no pharmacy claim for any IBD medication (aminosalicylates, enteral budesonide, thiopurines, and anti-TNFs), were considered to have a non-confirmed diagnosis of IBD. We did not include corticosteroids except enteral budesonide in this definition, since they are widely prescribed apart from IBD. In case of multiple hospitalizations with ICD-10 codes related to both Crohn's disease and ulcerative colitis, the most recent diagnosis at cohort entry was retained. The date of IBD diagnosis was defined as the earliest diagnosis date either from hospital discharge diagnosis from the PMSI or from LTD diagnosis of the SNIIRAM. Patients diagnosed with IBD before January 1, 2009 were referred to as prevalent cases of IBD while patients identified between January 1, 2009 and December 31, 2013 accounted for incident cases of IBD. This cohort has been extensively described elsewhere.[18,20]

Patients with HIV infection, congenital immunodeficiency, organ transplantation, and incident patients with a concomitant diagnosis of serious infection at the date of IBD diagnosis were excluded.

## Follow-up

Date of inclusion in the cohort was January 1, 2009 for prevalent cases and the date of IBD diagnosis for incident cases. Considering that IBD therapeutic management may be different after occurrence of cancer and that chemotherapy may lead to



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immunosuppression and increased risk of infection,[21] patients were censored at the date of any cancer diagnosis. Patients were followed until December 31, 2014, loss of follow-up, death, occurrence of serious infections or cancer, whichever occurred first. In case of loss to follow-up (defined as no more contact until December 31, 2014), end of follow-up was the last known contact date, defined by the last claim in the database.

## Drug exposure

In France, infliximab and adalimumab are dispensed in hospitals or private clinics. Adalimumab and thiopurines are dispensed by pharmacies for one month.[22] Patients who received infliximab were considered exposed for two months following the infusion, those who received adalimumab or thiopurines were considered exposed for one month following delivery. Drug exposures were assumed to start the day of the drug infusion or delivery. Combination therapy was defined as concomitant exposure to anti-TNFs and thiopurines. During follow-up, patients could be exposed successively to different treatment sequences and could therefore contribute to more than one group of drug exposure. Treatment withdrawal was defined by a period of at least two months, after the last day of exposure, without any new treatment delivery.

## Outcomes

Study outcome was any serious infection, defined as a diagnosis of infection requiring hospitalization (related ICD-10 codes as primary diagnosis). Within this database, the diagnoses of infection requiring hospitalization and the type of infection have been shown to be accurate in 97% and 98% of the cases, respectively.[23]

Serious infections were classified according to infection sites. These included pulmonary; gastrointestinal; skin; urinary tract; ear, nose and throat (ENT);



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musculoskeletal, and other infections (including sepsis, non-classified opportunistic and mycobacterial infections). Opportunistic infections were classified according to pathogens. These included viral; mycobacterial; bacterial; fungal, and parasitic infections. Supplementary tables 2 and 3 provide infection diagnoses and related ICD-10 codes according to infection sites and pathogens.

## Covariates

Two groups of covariates were considered. Time-fixed covariates were measured at cohort entry and included sex, age, disease duration (≥ 10 years, 0-10 years, incident patients), exposure to methotrexate and aminosalicylates in the preceding 6 months, IBD-related endoscopy and imaging in the preceding year, history of IBD-related hospitalization or surgery, comorbidities (based on data from hospitalization discharges, LTDs, and specific procedures or treatments, see details in supplementary table 1) including: history of cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, diabetes, cirrhosis, obesity, alcohol use disorder, smoking behavior, history of serious and opportunistic infections. Time-varying covariates, including IBD activity as measured by exposure to corticosteroids and occurrence of IBD-related hospitalization or surgery, were updated every month and six months, respectively. Since narcotics use has been associated with an increased risk of serious infections in patients with IBD,[9] we included narcotics prescription as a time-dependent variable, updated every three months.

## Statistical analyses

We used marginal structural Cox proportional hazard models[24] adjusted for the time-fixed and time-varying covariates listed above to compare the risks of serious and



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opportunistic infections associated with exposure to: (1) combination therapy versus anti-TNF monotherapy; (2) combination therapy versus thiopurine monotherapy; (3) anti-TNF monotherapy versus thiopurine monotherapy. Marginal structural models are appropriate in the presence of time-dependent covariates (such as exposure to corticosteroids and IBD activity) that might be associated with both exposure and outcomes[9,13] (time-dependent confounders) and could also be affected by past exposure to thiopurines and anti-TNFs. Weights calculation was performed as suggested by Cole and Hernan.[25] Detailed statistical method is provided in the supplementary appendix.

The main analysis was restricted to patients with no history of cancer and a confirmed diagnosis of IBD. Additional analyses included subgroups analyses stratified on age at cohort entry (18-64; 65 years or older) and IBD phenotype. Several other sensitivity analyses were performed to test the robustness of our results. First, we excluded patients with serious infection within 6 months prior to start of follow-up, to avoid including potential prevalent infections. Second, since non-melanoma skin cancer (NMSC) occurrence may not alter the therapeutic management of IBD, as other cancers may do, we did not censor time after NMSC occurrence in patients with NMSC during follow-up. Third, we excluded pneumococcal infections from the list of opportunistic infections, since the definition of opportunistic infections may differ across studies.[5] In addition, we performed sensitivity analyses restricted to incident cases of IBD or including patients with a non-confirmed IBD diagnosis or a medical history of cancer.

Analyses were performed using SAS (version 9.4) statistical software (SAS Institute).



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# Results

## Characteristics of the cohort

Among the 246 704 individuals aged 18 years or older identified with IBD before 2014, 190 694 were included in the main analysis (Figure 1). During follow-up, 128 285 (67.3%) had never been exposed to thiopurines and anti-TNFs, while 47 572 (24.9%), 26 255 (13.8%), and 12 023 (6.3%) had ever been exposed to thiopurine monotherapy, anti-TNF monotherapy, and combination therapy, respectively, accounting for 109 177, 57 835, and 11 143 person-years (PY) of follow-up.

Overall, patients were predominantly female (54.3%) with a mean age of 44.9 (SD 16.4) years at cohort entry. Half had a diagnosis of Crohn's disease (50.3%) and half ulcerative colitis (49.7%). One third were incident cases, while 22.0% had been diagnosed for at least 10 years. IBD-related complications had occurred within the 6 months preceding cohort entry in 4.3%. These characteristics differed according to subsequent treatment exposure during follow-up (Table 1). Patients unexposed to thiopurines and anti-TNFs had a mean age of 47.8 years; a majority of them had a longstanding, uncomplicated ulcerative colitis. Those exposed to thiopurines and/or anti-TNFs, were mostly younger than 40 years and recently diagnosed with Crohn's disease, and had substantial rates of IBD-related hospitalization or surgery at cohort entry.

## Incidence of serious and opportunistic infections

Overall, 8561 serious infections and 674 opportunistic infections occurred, resulting in incidence rates of 9.4 and 0.8 per 1000 PY, respectively.



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Overall incidence rates of serious infections ranged from 8.4 per 1000 PY in patients unexposed to thiopurines and anti-TNFs to 10.5, 18.9, and 22.4 per 1000 PY in those exposed to thiopurine monotherapy, anti-TNF monotherapy, and combination therapy, respectively (Table 2). In incident patients, cases of serious infections occurred after a mean duration of 303 (SD 369), 365 (SD 346), and 136 (SD 169) days of exposure to thiopurine monotherapy, anti-TNF monotherapy, and combination therapy, respectively. Serious infection cases mostly affected lung (24.2%), gastrointestinal tract (22.5%), and skin (17.2%) (Supplementary table 4). Among patients with serious infections, 337 (3.9%) died within the 3 months following infection occurrence.

Overall incidence rates of opportunistic infections ranged from 0.4 per 1000 PY in patients unexposed to thiopurines and anti-TNFs to 1.7, 2.1, and 4.1 per 1000 PY in those exposed to thiopurine monotherapy, anti-TNF monotherapy, and combination therapy, respectively. In incident patients, opportunistic infections occurred after a mean duration of 371 (SD 417), 262 (SD 243), and 165 (SD 219) days of exposure to thiopurine monotherapy, anti-TNF monotherapy, and combination therapy, respectively. Opportunistic infections were mostly due to viruses (38.9%), mycobacteria (25.4%), and bacteria (23.7%) (Supplementary table 5). Only five parasitic infections occurred. Twenty patients with opportunistic infections (3%) died within the 3 months following infection occurrence.

## Risk of serious infections according to IBD treatment exposure

Patients exposed to combination therapy, anti-TNF monotherapy or thiopurine monotherapy had increased risks of serious infections compared to patients unexposed to thiopurines and anti-TNFs (Supplementary table 6).



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Among exposed patients, combination therapy was associated with an increased risk of serious infections, compared to anti-TNF monotherapy (hazard ratio [HR], 1.23; 95% confidence interval [95% CI], 1.05-1.45) (Table 3). This increased risk tended to concern all infection sites except urinary tract and skin. Combination therapy was also associated with an increased risk of serious infections compared to thiopurine monotherapy (HR, 2.11; 95% CI, 1.80- 2.48), regardless of infection site.

Anti-TNF monotherapy was associated with an increased risk of serious infections compared to thiopurine monotherapy (HR, 1.71; 95% CI, 1.56-1.88), regardless of infection site.

## Risk of opportunistic infections according to IBD treatment exposure

Patients exposed to combination therapy, anti-TNF monotherapy or thiopurine monotherapy had increased risks of opportunistic infections compared to patients unexposed to thiopurines and anti-TNFs (Supplementary table 6).

Combination therapy was associated with an increased risk of opportunistic infections compared to anti-TNF monotherapy overall (HR, 1.96; 95% CI, 1.32-2.91) (Table 4). This increased risk concerned viral, mycobacterial, and bacterial infections. Combination therapy was also associated with an increased risk of opportunistic infections compared to thiopurine monotherapy, overall (HR, 2.11; 95% CI, 1.45-3.08), and for mycobacterial and bacterial infections.

Anti-TNF monotherapy was not associated with a significantly different risk of opportunistic infections compared to thiopurine monotherapy overall (HR, 1.08; 95% CI, 0.83-1.40). However, the risks of mycobacterial and bacterial infections were higher with anti-TNF monotherapy than with thiopurine monotherapy (HR, 1.98; 95%



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CI, 1.15-3.40 and 2.38; 95% CI, 1.23-4.58, respectively), and the risk of viral infections was lower (HR, 0.57; 95% CI, 0.38- 0.87).

### Subgroup and sensitivity analyses

Incidence rates of serious and opportunistic infections were increased in patients aged 65 or more, compared to younger patients. Specifically, the annual incidence of serious infection in patients aged 65 or more, exposed to anti-TNFs, either in monotherapy or combination therapy, was approximately 5% (Table 5). However, hazard ratios were similar in patients younger and older than 65 years (Table 6). Results were consistent across IBD subtype, and were unchanged after exclusion of gastrointestinal and mycobacterial infections. The various sensitivity analyses yielded consistent results (Supplementary table 7).

## Discussion

Based on a large population-based, nationwide cohort study, our findings suggest that among patients with IBD, the risks of serious and opportunistic infections are higher with combination therapy than with thiopurine monotherapy or anti-TNF monotherapy. In addition, the risks of serious infections and of mycobacterial as well as opportunistic bacterial infections are increased with anti-TNF monotherapy compared to thiopurine monotherapy. Yet, the risk of opportunistic infections with anti-TNF monotherapy does not differ from that of thiopurine monotherapy, due to a lower risk of opportunistic viral infections with anti-TNFs than with thiopurines.

Observational studies have provided conflicting results on the risk of infection related to anti-TNFs.[8–10] Such an inconsistency is likely to be related to differences in exposure definitions, comparators, and study populations considered. Indeed, most



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studies did not assess separately the risk related to anti-TNFs in combination therapy and monotherapy. In a recent Danish cohort study, an increased risk of serious infections was reported in anti-TNFs new users compared to patients non-exposed to anti-TNFs after adjustment for thiopurines use,[8] while another cohort study reported no increased risk of serious infections associated with anti-TNFs exposure as combination therapy or monotherapy, compared with patients treated with thiopurines.[10] A similar risk of serious infections with combination therapy compared to anti-TNF monotherapy was reported in a cohort study including new anti-TNFs users in Medicare.[14] However patients covered by Medicare are older than 65 or have chronic diseases; therefore these findings may only be applicable to this subgroup of patients. In addition, previous observational studies assessing the risk of infection associated with thiopurines and anti-TNFs in IBD did not concomitantly adjust for disease activity and corticosteroid exposure over time. Though, disease activity and corticosteroids are two major predictors of infection as shown in a US study based on the TREAT (Crohn's Therapy, Resource, Evaluation and Assessment Tool) registry,[9] and they may have an impact on treatment modification and occurrence of infection. To our knowledge, the present study, based on a large and unselected population, is the first to provide two-by-two comparisons of the risk of infections between the various immunosuppressive-based IBD treatment regimens, adjusting for both fixed and time-dependent covariates including IBD activity and exposure to corticosteroids.

We found that combination therapy and anti-TNF monotherapy were associated with an increased risk of almost all site-specific serious infections compared to thiopurine monotherapy. In the recent Danish study, an increased risk of serious infection was reported with anti-TNFs, although it was only statistically significant for skin



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infections.[8] Our findings suggest that anti-TNFs may be associated with an increased risk of infections, irrespective of the infection site, which is consistent with the fact that TNF has a central role in host response to infection, regardless of its site.

While several observational studies assessed the risk of opportunistic infections in patients with rheumatoid arthritis, very few included patients with IBD.[14,26,27] Although the definition of opportunistic infections may differ across studies, the rates of opportunistic infections reported in our study are in the range of those reported previously.[27,28] We found that exposure to anti-TNFs, either in combination or monotherapy was associated with increased risks of opportunistic bacterial and mycobacterial infections compared to thiopurine monotherapy. This is consistent with previous studies reporting increased risks of bacterial and mycobacterial infections related to anti-TNFs.[29,30] Moreover, combination therapy was associated with increased risks of opportunistic bacterial and mycobacterial infections compared to anti-TNF monotherapy, suggesting that the risks of opportunistic bacterial and mycobacterial infections are additionally increased by adding thiopurines to anti-TNFs, as reported in a meta-analysis of clinical trials.[31] The situation was different regarding opportunistic viral infections. Indeed, while combination therapy was associated with an increased risk of opportunistic viral infections compared to anti-TNF monotherapy, no difference was found compared to thiopurine monotherapy as a result of a lower risk with anti-TNFs than with thiopurines. This suggests that the risk of opportunistic viral infections under combination therapy is driven by thiopurines. Consistently, previous studies showed that thiopurines increase the risk of viral infections.[5]

Age is a major risk factor of serious and opportunistic infections.[9,26] After adjustment for major comorbidities and IBD disease activity, relative risks of serious or



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opportunistic infections were of similar magnitude, regardless of age. However, the absolute risks were 2- to 3-fold increased in patients aged 65 years or more as compared to younger patients.

The primary strength of our study is its nationwide, population-based cohort design. The database is comprehensive in that it includes all medical prescriptions and hospital stays for IBD in France, thus resulting in high number of patients exposed to the various therapeutic regimens used in real-life practice during the study period, including combination therapy. The most recent biological therapies, such as vedolizumab and ustekinumab were not considered since their marketing authorizations in inflammatory bowel disease were obtained in November 2014 and 2016, respectively, in France. Patients are unselected because universal access to healthcare is guaranteed for all French residents and there is no other universal insurance scheme in France. The sample size was large enough to adequately assess combination therapy as well as anti-TNF and thiopurines monotherapies. Finally, we assessed time dependent confounding variables such as IBD activity and corticosteroids exposure.

Some limitations should be noted. Until now, there has been no validation study of the ICD codes related to IBD in the SNIIRAM database. However, a descriptive study on the same cohort[18] reported treatment exposure, hospitalization, and surgery rates similar to current standard of care and incidence rates in the range of those reported in other populations.[32] Although identification of infection was based on discharge diagnosis only, the validity of our outcomes was recently assessed, with more than 95% accuracy of recorded cases and type of infections.[23] In addition, incidence rates of serious infections in patients exposed to anti-TNFs reported in our study are similar to those reported in the TREAT registry. The increased risk associated with



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thiopurines or anti-TNFs compared to unexposed patients reported in our study may also strengthen the external validity of our findings. It is also noteworthy that the inclusion of prevalent users of thiopurines and anti-TNFs in the main analysis (to ensure sufficient statistical power to assess the risk of opportunistic infections) may have caused a prevalent user bias, which could results in an underestimation of the risk. However, similar results were obtained in the analysis restricted to incident cases, suggesting that such a bias, if any, is limited. Lastly, the definition of active disease was based on a combined indicator including IBD-related hospitalization or surgery and exposure to corticosteroids. Although this definition may have excluded some mild cases of active disease only treated with aminosalicylates, this is unlikely to have biased our results since disease activity needs to be severe to increase the risk of serious infections as shown in the TREAT registry.[9]

In conclusion, these findings show that the various immunosuppressive-based IBD treatment regimens have heterogeneous risk profiles regarding the risks of serious and opportunistic infections. More specifically, combination therapy exposes to higher risks of serious and opportunistic infections than anti-TNF monotherapy, which exposes itself to higher risks of serious infections, and mycobacterial and opportunistic bacterial infections than thiopurine monotherapy. The risks of infection should therefore be taken into consideration and weighed against potential benefits of the various treatment options for IBD management.



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Figure Legends:

Figure 1. Study Population Flowchart

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Author names in bold designate shared co-first authorship.



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**Table 1.** Patients characteristics at cohort entry according to subsequent treatment exposure during follow-up [a]

| | Unexposed to thiopurines and anti-TNFs (n=128 285) | Exposed to thiopurine monotherapy (n=47 572) | Exposed to anti-TNF monotherapy (n=26 255) | Exposed to combination therapy (n=12 023) |
|---|---|---|---|---|
| Total treatment duration (days), mean (SD) | - | 508 (595) | 547 (580) | 238 (281) |
| Age at cohort inclusion, mean (SD) | 47.8 (16.5) | 39.1 (14.6) | 36.9 (13.6) | 34.4 (12.7) |
| Male sex, n (%) | 58 705 (45.8) | 21 899 (46.0) | 11 520 (43.9) | 5498 (45.7) |
| Complementary universal health insurance [b], n (%) | 10 202 (8.0) | 5260 (11.1) | 3497 (13.3) | 1673 (13.9) |
| Inflammatory bowel disease subtype, n (%) | | | | |
| Crohn's disease | 53 773 (41.9) | 30 914 (65.0) | 19 592 (74.6) | 8665 (72.1) |
| Ulcerative colitis | 74 512 (58.1) | 16 658 (35.0) | 6663 (25.4) | 3358 (27.9) |
| Age at IBD diagnosis, mean (SD) | 42.1 (16.4) | 34.1 (14.0) | 32.1 (13.3) | 30.3 (12.4) |
| Disease duration at cohort entry, n (%) | | | | |
| ≥ 10 years | 30 237 (23.6) | 8686 (18.3) | 4547 (17.3) | 1716 (14.3) |
| 0-10 years | 56 310 (43.9) | 22 369 (47.0) | 12 414 (47.3) | 5520 (45.9) |
| Incident patients | 41 738 (32.5) | 16 517 (34.7) | 9294 (35.4) | 4787 (39.8) |
| Inflammatory bowel disease drugs [c], n (%) | | | | |
| Corticosteroids | 12 668 (9.9) | 7190 (15.1) | 4490 (17.1) | 1989 (16.5) |
| Methotrexate | 1216 (0.9) | 237 (0.5) | 1399 (5.3) | 156 (1.3) |
| Aminosalicylates | 57 115 (44.5) | 19 191 (40.3) | 9509 (36.2) | 4470 (37.2) |
| IBD disease activity assessment [c], n (%) | | | | |
| Digestive endoscopy | 55 272 (34.9) | 17 757 (37.3) | 10 384 (39.6) | 4943 (41.1) |
| Radiology tests | 19 824 (12.5) | 8030 (16.9) | 5850 (22.3) | 2699 (22.4) |
| Complications related to IBD [c], n (%) | | | | |
| Surgery related to IBD | 930 (0.7) | 946 (2.0) | 909 (3.5) | 470 (3.9) |
| Hospitalization related to IBD | 1819 (1.4) | 3858 (8.1) | 2838 (10.8) | 1631 (13.6) |
| Comorbidities, n (%) | | | | |
| Cardiovascular disease | 7713 (6.0) | 1734 (3.6) | 878 (3.3) | 318 (2.6) |
| Cerebrovascular disease | 2943 (2.3) | 586 (1.2) | 279 (1.1) | 119 (1.0) |
| Chronic pulmonary disease | 8243 (6.4) | 2398 (5.0) | 1466 (5.6) | 548 (4.6) |
| Chronic kidney disease | 1418 (1.1) | 296 (0.6) | 205 (0.8) | 63 (0.5) |
| Diabetes | 9866 (7.7) | 2285 (4.8) | 1009 (3.8) | 389 (3.2) |
| Cirrhosis | 607 (0.5) | 140 (0.3) | 126 (0.5) | 39 (0.3) |
| Obesity | 1924 (1.5) | 593 (1.2) | 399 (1.5) | 153 (1.3) |
| Alcohol use disorder | 2288 (1.8) | 619 (1.3) | 357 (1.4) | 135 (1.1) |
| Smoking behavior | 3701 (2.9) | 1804 (3.8) | 1388 (5.3) | 505 (4.2) |
| History of serious infections | 3265 (2.5) | 1076 (2.3) | 839 (3.2) | 317 (2.6) |
| History of opportunistic infections | 218 (0.2) | 103 (0.2) | 79 (0.3) | 34 (0.3) |

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| | | | | |
|---|---|---|---|---|
| Narcotics use [c], n (%) | 25 301 (16.0) | 7845 (16.5) | 5275 (20.1) | 2105 (17.5) |

[a] Patients exposed to more than one exposure group during follow-up were considered in each corresponding group. [b] Free access to healthcare for people with an annual income <50% of poverty threshold. [c] As registered within six months before cohort entry (except for IBD disease activity assessment [within one year])

**Table 2.** Incidence of serious and opportunistic infections according to treatment exposure during follow-up, overall and by infection site and pathogen

| | **Unexposed to thiopurines and anti-TNFs** 719 407 person-years | **Exposed to thiopurine monotherapy** 109 177 person-years | **Exposed to anti-TNF monotherapy** 57 835 person-years | **Exposed to combination therapy** 11 143 person-years |
|---|---|---|---|---|
| Serious infections, overall | 6067 (8.4) | 1149 (10.5) | 1095 (18.9) | 250 (22.4) |
| Pulmonary infections | 1554 (2.2) | 230 (2.1) | 236 (4.1) | 55 (4.9) |
| GI infections | 1372 (1.9) | 286 (2.6) | 213 (3.7) | 54 (4.8) |
| Skin infections | 994 (1.4) | 201 (1.8) | 234 (4.0) | 47 (4.2) |
| Urinary tract infections | 918 (1.3) | 142 (1.3) | 148 (2.6) | 25 (2.2) |
| ENT infections | 174 (0.2) | 41 (0.4) | 39 (0.7) | 9 (0.8) |
| Musculoskeletal infections | 161 (0.2) | 27 (0.2) | 24 (0.4) | 8 (0.7) |
| Other infections | 894 (1.2) | 222 (2.0) | 201 (3.5) | 52 (4.7) |
| Opportunistic infections, overall | 322 (0.4) | 187 (1.7) | 119 (2.1) | 46 (4.1) |
| Viral infections | 84 (0.1) | 122 (1.1) | 41 (0.7) | 15 (1.3) |
| Mycobacterial infections | 87 (0.1) | 32 (0.3) | 36 (0.6) | 16 (1.4) |
| Bacterial infections | 96 (0.1) | 21 (0.2) | 31 (0.5) | 12 (1.1) |
| Fungal infections | 51 (0.1) | 12 (0.1) | 10 (0.2) | 3 (0.3) |

Numbers are n (incidence rates/1000 person-years)

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**Table 3.** Multivariable Adjusted Hazard Ratios (and 95% confidence interval) [a] of serious infections according to medication exposure, overall and by infection site

| | Exposed to combination therapy versus anti-TNF monotherapy | Exposed to combination therapy versus thiopurine monotherapy | Exposed to anti-TNF monotherapy versus thiopurine monotherapy |
|---|---|---|---|
| Serious infections, overall | 1.23 (1.05-1.45) | 2.11 (1.80-2.48) | 1.71 (1.56-1.88) |
| Pulmonary infections | 1.40 (0.99-1.98) | 3.14 (2.24-4.40) | 2.24 (1.83-2.75) |
| GI infections | 1.34 (0.93-1.93) | 1.84 (1.30-2.60) | 1.37 (1.12-1.68) |
| Skin infections | 1.08 (0.76-1.54) | 1.86 (1.30-2.68) | 1.72 (1.38-2.15) |
| Urinary tract infections | 0.89 (0.56-1.41) | 1.69 (1.07-2.67) | 1.90 (1.47-2.45) |
| ENT infections | 1.47 (0.60-3.59) | 1.95 (0.80-4.73) | 1.32 (0.83-2.12) |
| Musculoskeletal infections | 1.89 (0.78-4.55) | 2.58 (1.07-6.23) | 1.36 (0.68-2.73) |
| Other infections | 1.26 (0.89-1.79) | 2.03 (1.44-2.87) | 1.61 (1.29-2.01) |

[a] For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section

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**Table 4.** Multivariable Adjusted hazard ratios (and 95% confidence interval) [a] of opportunistic infections according to medication exposure, overall and by pathogen

| | Exposed to combination therapy versus anti-TNF monotherapy | Exposed to combination therapy versus thiopurine monotherapy | Exposed to anti-TNF monotherapy versus thiopurine monotherapy |
|---|---|---|---|
| Opportunistic infections, overall | 1.96 (1.32-2.91) | 2.11 (1.45-3.08) | 1.08 (0.83-1.40) |
| Viral infections | 1.98 (1.00-3.94) | 1.13 (0.62-2.08) | 0.57 (0.38-0.87) |
| Mycobacterial infections | 2.17 (1.08-4.36) | 4.30 (2.10-8.80) | 1.98 (1.15-3.40) |
| Bacterial infections | 1.99 (0.99-4.01) | 4.73 (2.10-10.7) | 2.38 (1.23-4.58) |
| Fungal infections | 0.78 (0.21-2.88) | 0.96 (0.26-3.61) | 1.24 (0.49-3.16) |

[a] For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section

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**Table 5.** Incidence of serious and opportunistic infections according to age category at cohort entry

| | **Unexposed to thiopurines and anti-TNFs**<br>18-64 years: 627 683 PY<br>≥ 65 years: 91 724 PY | **Exposed to thiopurine monotherapy**<br>18-64 years: 102 593 PY<br>≥ 65 years: 6584 PY | **Exposed to anti-TNF monotherapy**<br>18-64 years: 55 975 PY<br>≥ 65 years: 1860 PY | **Exposed to combination therapy**<br>18-64 years: 10 905 PY<br>≥ 65 years: 238 PY |
|---|---|---|---|---|
| Serious infections, overall | | | | |
| 18-64 years | 3954 (6.3) | 972 (9.5) | 996 (17.8) | 238 (21.8) |
| ≥ 65 years | 2113 (23.0) | 177 (26.9) | 99 (53.2) | 12 (50.5) |
| Opportunistic infections, overall | | | | |
| 18-64 years | 231 (0.4) | 169 (1.6) | 108 (1.9) | 44 (4.0) |
| ≥ 65 years | 91 (1.0) | 18 (2.7) | 11 (5.9) | 2 (8.4) |

Numbers are n (incidence rates/1000 PY [person-years])

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**Table 6.** Multivariable Adjusted hazard ratios (and 95% confidence interval) a for any serious or opportunistic infections according to medication exposure and age category at cohort entry

| | **Exposed to combination therapy versus anti-TNF monotherapy** | **Exposed to combination therapy versus thiopurine monotherapy** | **Exposed to anti-TNF monotherapy versus thiopurine monotherapy** |
|---|---|---|---|
| Serious infections, overall | | | |
| 18-64 years | 1.20 (1.02-1.42) | 1.98 (1.68-2.34) | 1.65 (1.49-1.83) |
| ≥ 65 years | 1.34 (0.64-2.80) | 2.30 (1.14-4.65) | 1.71 (1.28-2.29) |
| Opportunistic infections, overall | | | |
| 18-64 years | 1.95 (1.30-2.93) | 2.02 (1.37-2.96) | 1.03 (0.78-1.36) |
| ≥ 65 years | 1.78 (0.37-8.59) | 2.41 (0.53-11.0) | 1.35 (0.56-3.27) |

[a] For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section.

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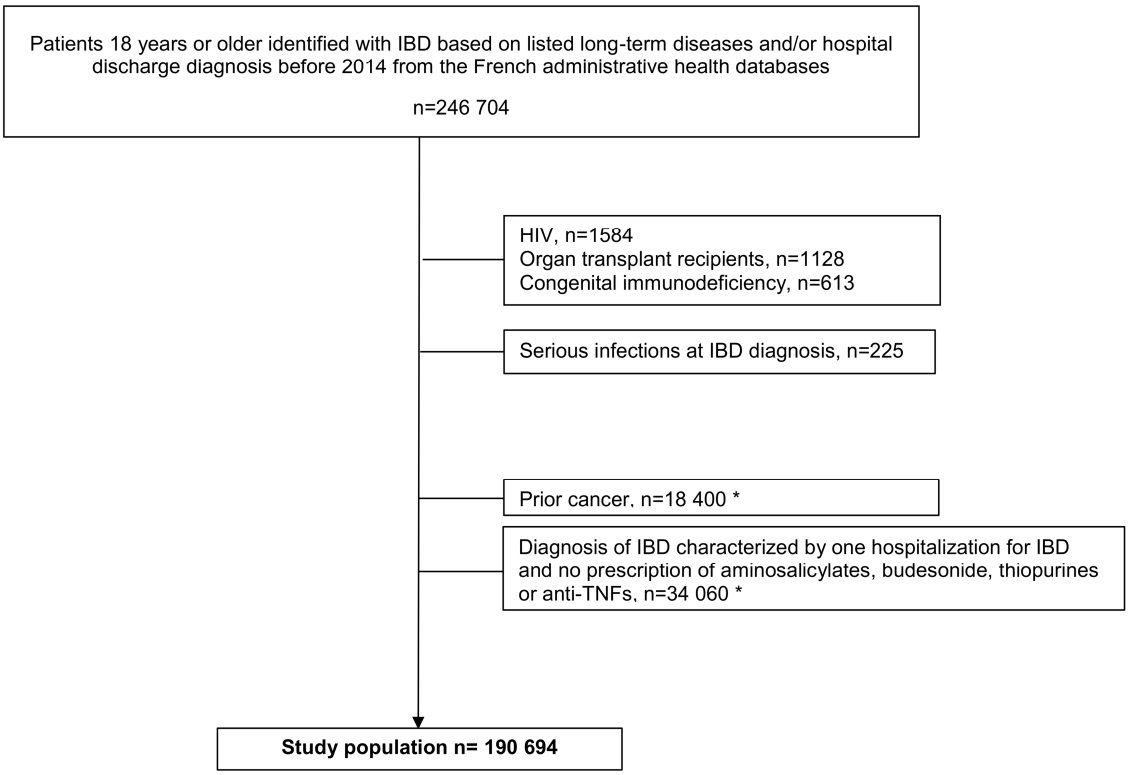


*Considered in sensitivity analyses

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Supplementary Material

Appendix: Methods

Supplementary table 1: Codes used to define exclusion criteria and covariates

Supplementary table 2: All diagnoses of infections with related ICD 10-codes included as any serious infection with the subdivision into site-specific groups

Supplementary table 3: All diagnoses of infections with related ICD 10-codes included as any opportunistic infection with the subdivision into pathogen-specific groups

Supplementary table 4: Characterization of serious infection cases

Supplementary table 5: Characterization of opportunistic infection cases

Supplementary table 6: Multivariable Adjusted Hazard Ratios (and 95% confidence interval) of serious and opportunistic infections according to treatment exposure (reference group: unexposed to thiopurines and anti-TNFs), overall and by infection site and pathogen

Supplementary table 7: Multivariable Adjusted hazard ratios (and 95% confidence interval) of serious and opportunistic infections according to treatment exposure by IBD subtype and in sensitivity analyses



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**Appendix: Methods**

Under the assumption of no unmeasured confounders, we used marginal structural models to estimate causal effects of thiopurines and anti-TNFs on the risk of serious infections.[1] These models, adjusted for time-dependent covariates with inverse probability treatment weights, are appropriate in the presence of time-dependent covariates (such as exposure to corticosteroids and IBD activity) that might be associated with both prescription of thiopurines or anti-TNFs and outcomes (time-dependent confounders) and could also be affected by past exposure to thiopurines and anti-TNFs.

The conditional probability of receiving observed treatment was estimated using multinomial logistic regression with generalized logit link. Covariates included were the baseline and time-dependent covariates (listed in Table 1) and past treatment history.

Weights from the exposure selection model were calculated as follows: the numerator was the probability of receiving the treatment actually received after treatment modification conditional on baseline covariates and past treatment history. The denominator was the predicted probability of receiving the treatment actually received after treatment modification conditional on baseline covariates, past treatment history and time-varying covariates.

To adjust for potential selection bias from loss to follow-up, we similarly modeled the propensity to be censored. Binary logistic regression was used for the censoring model. Weights from the censoring model were calculated as follows: the numerator was the probability of being censored conditional on baseline covariates and past treatment history. The denominator was the predicted probability of being censored conditional on baseline covariates, past treatment history and time-varying covariates.

The stabilized weights were the product of the weights from the exposure selection and the censoring models, updated at each time interval. After calculation, the weights were truncated at 1st and 99$^{th}$ percentiles to minimize the impact of extreme weights and improve precision.[2,3]

In the main analysis, stabilized weights using inverse probability of treatment and inverse probability of censoring were calculated at each treatment modification, since treatment assignment was continuously recorded rather than during scheduled follow-up visits. It may also provide a precise estimation of drug exposure, notably treatment introduction, while the increased risk of serious infections associated with anti-TNFs was mostly observed right after treatment introduction.[4] In a complementary analysis, we discretized the time scale on periods of one month for the estimation of the weights and results were shown to be consistent.
After truncation at the 1$^{st}$ percentile (0.43) and 99$^{th}$ percentile (3.43), Mean (SD) of the weights were 1.02 (0.39). There was no tendency for the mean to deviate from 1 after a long period of follow-up.

The outcome analysis model was adjusted for baseline covariates. Robust variance estimators were used to estimate conservative 95% confidence intervals.

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**Supplementary table 1: Codes used to define exclusion criteria and covariates**

| Comorbidity | ICD-10 codes | Anatomical Therapeutic Chemical (ATC) classification system code | French Medical Common Procedure Coding System |
|---|---|---|---|
| Exclusion criteria | | | |
| Cancer | C00-C97 | - | - |
| Congenital deficiency | D80-D84 | J06BA02, J06BA01 | - |
| HIV | B20-B24, F024, O987, R75, Z206, Z21 | J05AX07, J05AX08, J05AX09, J05AX10, J05AX11, J05AE (except J05AE12), J05AF (except J05AF10), J05AG, J05AR | - |
| Organ transplantation | T86.0-T86.4, T86.80-T86.82, T86.9, Z94.0-Z94.4,Z94.803, Z94.804, Z94.809, Z94.81, Z94.82, Z94.88, Z94.9 | - | HNEA002,DZEA001, DZEA002, DZEA003, DZEA004, DZFA004, FELF009, GFEA001, GFEA002, GFEA003, GFEA004, GFEA005, GFEA006, GFEA007, HGEA002, HGEA004, HGEA005, HLEA001, HLEA002, HNEA900, JAEA003 |
| | | | |
| Covariates | | | |
| Cardiovascular disease | I11.0; I13.0; I13.2; I0-I3; I40-I43; I50; J81 | - | - |
| Cerebrovascular disease | I60-I69; G45 | - | - |
| Chronic pulmonary disease | J4-J7; J82-J84; J96.0; J96.1 | R03AC, R03B | - |
| Chronic kidney disease | I120; I131; N18-N19; Y84.1; Z49 | - | - |
| Diabetes | E11-E14 | | - |
| Cirrhosis | I85; I86.4; I98.2; I98.3; K70.0; K70.3-K70.4; K71.1; K71.7; K72; K74.4-K74.6; K76.6; K76.7; | - | - |
| Obesity | E66 | - | - |
| Alcohol use disorder | E24.4; G31.2; G62.1; G72.1; I42.6; K29.2: K70; K86.0; Z50.2; Z71.4; Z12.1 | - | - |
| Smoking behavior | F17; Z71.6; Z72.0 | - | - |
| IBD-related hospitalization | K50; K51; K56; K60; K61 | - | - |
| IBD-related surgery | | | |
| Colectomy | - | - | HHFA002, HHFA004, HHFA005, HHFA006, HHFA008, HHFA009, HHFA010, HHFA014, HHFA017, HHFA018, HHFA021, HHFA022, HHFA023, HHFA024, HHFA026, HHFA028, HHFA029, HHFA030, HHFA031 |
| Intestinal resection | - | - | HGCA005, HGCC015, HGFA003, HGFA004, HGFA005, HGFA007, HGFC014, HGFC016, HGFC021 |
| Perineal surgery and minor digestive surgery | - | - | HKPA004, HKPA005, HKPA006, HKPA007, HKPA008, HGCA008, HGCC026, HGLA001, HHCA003, HHCC011, HPPA002, HPPC003, ZCJA002, ZCJA004 |



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**Supplementary table 2: All diagnoses of infections with related ICD 10-codes included as any serious infection with the subdivision into site-specific groups**

| Subgroup of infection | Diagnoses | ICD-10 |
|---|---|---|
| | | |
| Pulmonary infections | Pneumonia | A48.1; B01.2; B05.2; B25.0; J12-J18; J10-J11 |
| | Other acute lower respiratory infections | A37; A42.0; B39-B40; B44; B58.3; B59; B95.3; J20-J22; U04 |
| | Abscessus pulmonis | J85 |
| | Empyema pleurae | J86 |
| | | |
| GI infections | Intestinal infectious disease | A00-A08; K93.820 |
| | Viral hepatitis | B15; B17; B25.1 |
| | Cholangitis | K80-K810; K830, K87.00; B25.8 |
| | Liver abscess | K750 |
| | Infectious esophagitis | B00.8(K23.80) |
| | | |
| Skin and subcutaneous tissue infections | Erysipelas | A46 |
| | Dermatophytosis and other superficial mycoses | B35-B36 |
| | Cellulitis and abscess | L02-L03 |
| | Herpes virus | B00.1-B00.2; B00.7; B00.9; B01.8-B01.9; B02.3-B02.9; B05.3-B05.9; B06.8-B06.9; B08-B09; A60; |
| | Other local infections of skin, oral tissue and subcutaneous tissue | A36.3; K11.3-K12.2; L00-L01;L04-L05; L08; L30.3; M72.6 |
| | | |
| Urinary tract infections | Nephritis | N10 |
| | Acute prostatitis and prostate abscess | N41.0; N41.2; N41.3 |
| | Cystitis | N30.0 |
| | Salpingitis and oophoritis | N70.0 |
| | Endometritis | N71.0 |
| | Cervicitis uteri | N72 |
| | Syphilis | A50-A53; I98.0 |
| | Gonorrhea | A54 |
| | Chlamydia | A55-A56 |
| | Orchitis and epididymitis | N45 |
| | Other Urinary tract infections | N39.0; N73.3; N77.1 |



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| Subgroup of infection | Diagnoses | ICD-10 |
|---|---|---|
| ENT infections | Mastoiditis | H70 |
| | Nasopharyngitis | A36.1 |
| | Sinusitis | J01 |
| | Pharyngitis | J02 |
| | Pharyngeal, retropharyngeal and parapharyngeal abscess | J36;J39.0-J39.1 |
| | Tonsillitis | A36.0; J03 |
| | Laryngitis and tracheitis | A36.2; J04-J05; J37 |
| | Acute upper respiratory infections of multiple and unspecified sites | A36.8-A36.9; J06 |
| | Infection of external ear and acute otitis media | H60.0-H60.3; H65.1-H65.2; H66; H68.0 |
| | | |
| Musculoskeletal infections | Infectious arthritis | M00-M01 |
| | Infective myositis | M60.0 |
| | Osteomyelitis | M86 |
| | | |
| Other infections | Infection of the eye | B00.5; B30; H00-H01; H03.1; H06.1; H10.5; H10.8; H13.1; H19.1-H19.2 |
| | Infections in the nervous system | A32.1; A39; A80-A89; B00.3-B00.4; B01.0-B01.1; B02.0-B02.2; B05.0-B05.1; B06.0; G00-G02; G04-G07 |
| | Infections of prosthetic devices, implants and grafts | T82.6-T82.7; T84.5-T84.7; T85.7 |
| | Sepsis, systemic inflammatory response syndrome (SIRS) of infectious origin and septic shock | A32.7; A40-A41; R57.2; R65.0-R65.1 |
| | Certain bacterial disease | A20-A28; A32; A34-A35; A38; A42-A44; A48.0; A48.2-A49.9; B95.1; B95.2; B95.4-B95.8; B96-B97 |
| | Spirochaetal disease | A65-A69 |
| | Rickettsiosis | A75-A79 |
| | Viral infections | A90-A99; B25.2; B25.9; B26-B27; B33-B34 |
| | Mycoses | B37-B49 |
| | Protozoal diseases | B50-B57; B58.1-B58.2; B58.8-B58.9; B60-B83; |
| | Unspecified infectious diseases | B99.9 |
| | Acute infective pericarditis and endocarditis | I30.1; I33.0 |
| | Mycobacterial infections | A15-A19; A31; K23.0; K67.3; K93.0 ;M01.1; M49.0; M90.0 ; N33.0; N74.0; N74.1 |



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**Supplementary table 3: All diagnoses of infections with related ICD 10-codes included as any opportunistic infection with the subdivision into pathogen-specific groups**

| Subgroup of infection | Diagnoses | ICD-10 |
|---|---|---|
| | | |
| Viral infections | Cytomegalovirus | B25; B27.1 |
| | Herpes virus | B00-B02; A60.0 |
| | Epstein–Barr virus | B27.0 |
| | Progressive multifocal leukoencephalopathy | A81.2 |
| | Acute viral hepatitis unspecified | B17.9 |
| | Viral meningitis | G02.0 |
| | Viral pneumoniae | J17.1 |
| | | |
| Mycobacterial infections | Mycobacterial infections | A15-A19; A31; K23.0; K67.3; K93.0; M01.1; M49.0; M90.0; N33.0; N74.0; N74.1 |
| | | |
| Bacterial infections | Bartonellosis | A44 |
| | Legionnaires' disease | A48.1-A48.2 |
| | Pneumonia and sepsis due to Streptococcus pneumoniae | A40.3; J13; B95.3 |
| | Nocardiosis | A43 |
| | Actinomycosis | A42 |
| | Listeriosis | A32 |
| | Salmonella infections | A02 |
| | | |
| Fungal infections | Candidiasis | B37 |
| | Coccidioidomycosis | B38 |
| | Histoplasmosis | B39 |
| | Blastomycosis | B40 |
| | Aspergillosis | B44 |
| | Cryptococcosis | B45 |
| | Pneumocystosis | B59 |
| | Fungal meningitis | G02.1 |
| | Fungal pneumoniae | J17.2 |
| | | |
| Parasitic infections | Cryptosporidiosis | A07.2 |
| | Isosporiasis | A07.3 |
| | Leishmaniasis | B55 |
| | Toxoplasmosis | B58 |
| | Strongyloidiasis | B78 |
| | | |



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**Supplementary table 4: Characterization of serious infection cases**

| Subgroup of infection | Diagnoses | n (%) |
|---|---|---|
| | | |
| Pulmonary infections | | 2075(24.2) |
| | Pneumonia | 1733(20.2) |
| | Other acute lower respiratory infections | 307(3.6) |
| | Abscessus pulmonis | 20(0.2) |
| | Empyema pleurae | 15(0.2) |
| | | |
| GI infections | | 1925(22.5) |
| | Intestinal infectious disease | 689(8.0) |
| | Viral hepatitis | 54(0.6) |
| | Cholangitis | 1142(13.3) |
| | Liver abscess | 35(0.4) |
| | Infectious esophagitis | 5(0.1) |
| | | |
| Skin and subcutaneous tissue infections | | 1476(17.2) |
| | Erysipelas | 271(3.2) |
| | Dermatophytosis and other superficial mycoses | 5(0.1) |
| | Cellulitis and abscess | 745(8.7) |
| | Herpes virus | 111(1.3) |
| | Other local infections of skin, oral tissue and subcutaneous tissue | 344(4.0) |
| | | |
| Urinary tract infections | | 1233(14.4) |
| | Nephritis | 602(7.0) |
| | Acute prostatitis and prostate abscess | 177(2.1) |
| | Cystitis | 90(1.1) |
| | Salpingitis and oophoritis | 95(1.1) |
| | Endometritis | 12(0.1) |
| | Cervicitis uteri | 5(0.1) |
| | Syphilis | 9(0.1) |
| | Gonorrhea | 1(0.0) |
| | Chlamydia | 4(0.0) |
| | Orchitis and epididymitis | 50(0.6) |
| | Other Urinary tract infections | 188(2.2) |
| | | |



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| Subgroup of infection | Diagnoses | n (%) |
|---|---|---|
| ENT infections | | 263(3.1) |
| | Mastoiditis | 4(0.0) |
| | Nasopharyngitis | 0 |
| | Sinuitis | 74(0.9) |
| | Pharyngitis | 41(0.5) |
| | Pharyngeal, retropharyngeal and parapharyngeal abscess | 81(0.9) |
| | Tonsillitis | 13(0.2) |
| | Laryngitis and tracheitis | 13(0.2) |
| | Acute upper respiratory infections of multiple and unspecified sites | 4(0.0) |
| | Infection of external ear and acute otitis media | 33(0.4) |
| | | |
| Musculoskeletal infections | | 220(2.6) |
| | Infectious arthritis | 120(1.4) |
| | Infective myositis | 31(0.4) |
| | Osteomyelitis | 69(0.8) |
| | | |
| Other infections | | 1369(16.0) |
| | Infection of the eye | 9(0.1) |
| | Infections in the nervous system | 133(1.6) |
| | Infections of prosthetic devices, implants and grafts | 90(1.1) |
| | Sepsis, systemic inflammatory response syndrome (SIRS) of infectious origin and septic shock | 611(7.1) |
| | Certain bacterial disease | 27(0.3) |
| | Spirochaetal disease | 15(0.2) |
| | Rickettsiosis | 6(0.1) |
| | Viral infections | 114(1.3) |
| | Mycoses | 27(0.3) |
| | Protozoal diseases | 19(0.2) |
| | Unspecified infectious diseases | 87(1.0) |
| | Acute infective pericarditis and endocarditis | 56(0.7) |
| | Mycobacterial infections | 175(2.0) |
| | | |



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**Supplementary table 5: Characterization of opportunistic infection cases**

| Subgroup of infection | Diagnoses | n (%) |
|---|---|---|
| | | |
| Viral infections | | 262(38.9) |
| | Cytomegalovirus | 104(15.4) |
| | Herpes virus | 104(15.4) |
| | Epstein–Barr virus | 26(3.9) |
| | Progressive multifocal leukoencephalopathy | 1(0.1) |
| | Acute viral hepatitis unspecified | 3(0.4) |
| | Viral meningitis | 17(2.5) |
| | Viral pneumoniae | 7(1.0) |
| | | |
| Mycobacterial infections | | 171(25.4) |
| | | |
| Bacterial infections | | 160(23.7) |
| | Bartonellosis | 0 |
| | Legionnaires' disease | 25(3.7) |
| | Pneumonia and sepsis due to Streptococcus pneumoniae | 82(12.2) |
| | Nocardiosis | 0 |
| | Actinomycosis | 0 |
| | Listeriosis | 10(1.5) |
| | Salmonella infections | 43(6.4) |
| | | |
| Fungal infections | | 76(11.3) |
| | Candidiasis | 36(5.3) |
| | Coccidioidomycosis | 0 |
| | Histoplasmosis | 0 |
| | Blastomycosis | 0 |
| | Aspergillosis | 18(2.7) |
| | Cryptococcosis | 0 |
| | Pneumocystosis | 13(1.9) |
| | Fungal meningitis | 0 |
| | Fungal pneumoniae | 9(1.3) |
| | | |
| Parasitic infections | | 5(0.7) |
| | Cryptosporidiosis | 0 |
| | Isosporiasis | 0 |
| | Leishmaniasis | 2(0.3) |
| | Toxoplasmosis | 3(0.4) |
| | Strongyloidiasis | 0 |
| | | |



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**Supplementary table 6: Multivariable Adjusted Hazard Ratios (and 95% confidence interval) [a] of serious and opportunistic infections according to treatment exposure (reference group: unexposed to thiopurines and anti-TNFs), overall and by infection site and pathogen**

| | | Exposed to combination therapy versus unexposed to thiopurines or anti-TNFs | Exposed to anti-TNF monotherapy versus unexposed to thiopurines or anti-TNFs | Exposed to thiopurine monotherapy versus unexposed to thiopurines or anti-TNFs |
|---|---|---|---|---|
| | | | | |
| Serious infections, overall | | 2.79 (2.40-3.25) | 2.26 (2.08-2.45) | 1.32 (1.23-1.42) |
| | Pulmonary infections | 3.98 (2.89-5.49) | 2.85 (2.41-3.36) | 1.27 (1.09-1.48) |
| | GI infections | 2.53 (1.81-3.53) | 1.89 (1.57-2.26) | 1.37 (1.19-1.58) |
| | Skin infections | 2.31 (1.64-3.25) | 2.14 (1.78-2.56) | 1.24 (1.04-1.47) |
| | Urinary tract infections | 1.97 (1.27-3.05) | 2.21 (1.79-2.74) | 1.17 (0.96-1.42) |
| | ENT infections | 2.59 (1.11-6.05) | 1.76 (1.15-2.70) | 1.33 (0.93-1.89) |
| | Musculoskeletal infections | 3.42 (1.55-7.54) | 1.81 (1.02-3.22) | 1.33 (0.86-2.04) |
| | Other infections | 3.15 (2.26-4.39) | 2.49 (2.04-3.04) | 1.55 (1.31-1.83) |
| | | | | |
| Opportunistic infections, overall | | 7.86 (5.41-11.4) | 4.01 (3.06-5.26) | 3.72 (3.02-4.58) |
| | Viral infections | 10.2 (5.49-19.0) | 5.16 (3.22-8.26) | 9.01 (6.61-12.3) |
| | Mycobacterial infections | 9.15 (4.71-17.8) | 4.21 (2.58-6.86) | 2.13 (1.34-3.38) |
| | Bacterial infections | 8.95 (4.45-18.0) | 4.49 (2.71-7.43) | 1.89 (1.09-3.27) |
| | Fungal infections | 1.47 (0.38-5.68) | 1.90 (0.75-4.80) | 1.53 (0.65-3.60) |
| | | | | |

[a] For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section.



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**Supplementary table 7: Multivariable Adjusted hazard ratios (and 95% confidence interval) [a] of serious and opportunistic infections according to treatment exposure by IBD subtype and in sensitivity analyses**

| | Exposed to combination therapy versus anti-TNF monotherapy | Exposed to combination therapy versus thiopurine monotherapy | Exposed to anti-TNF monotherapy versus thiopurine monotherapy |
|---|---|---|---|
| **Serious infections, overall** | 1.23 (1.05-1.45) | 2.11 (1.80-2.48) | 1.71 (1.56-1.88) |
| IBD subtype | | | |
| Crohn's disease | 1.17 (0.96-1.43) | 2.00 (1.64-2.44) | 1.70 (1.52-1.91) |
| Ulcerative colitis | 1.32 (1.00-1.74) | 2.48 (1.91-3.22) | 1.88 (1.58-2.25) |
| Analysis excluding patients with serious infection within 6 months prior to start of follow-up | 1.22 (1.03-1.45) | 2.13 (1.80-2.52) | 1.74 (1.58-1.93) |
| Analysis non censoring patients with non-melanoma skin cancer during follow-up | 1.24 (1.05-1.45) | 2.12 (1.81-2.48) | 1.71 (1.56-1.88) |
| Analysis restricted to incident patients | 1.41 (1.07-1.84) | 2.29 (1.76-2.98) | 1.63 (1.36-1.94) |
| Analysis including patients with a medical history of cancer and patients with a non-confirmed IBD diagnosis [b] | 1.26 (1.07-1.48) | 2.21 (1.89-2.59) | 1.75 (1.59-1.93) |
| Serious infections, excluding GI infections | 1.21 (1.01-1.45) | 2.21 (1.84-2.64) | 1.82 (1.63-2.03) |
| **Opportunistic infections, overall** | 1.96 (1.32-2.91) | 2.11 (1.45-3.08) | 1.08 (0.83-1.40) |
| IBD subtype | | | |
| Crohn's disease | 1.88 (1.13-3.13) | 1.91 (1.17-3.12) | 1.02 (0.74-1.39) |
| Ulcerative colitis | 1.91 (1.01-3.61) | 2.73 (1.54-4.85) | 1.43 (0.89-2.29) |
| Analysis excluding patients with serious infection within 6 months prior to start of follow-up | 1.99 (1.33-2.98) | 2.17 (1.47-3.19) | 1.09 (0.83-1.44) |
| Analysis non censoring patients with non-melanoma skin cancer during follow-up | 1.94 (1.31-2.88) | 2.10 (1.45-3.06) | 1.08 (0.83-1.41) |
| Analysis restricted to incident patients | 1.84 (0.99-3.43) | 1.92 (1.05-3.51) | 1.04 (0.65-1.68) |
| Analysis including patients with a medical history of cancer and patients with a non-confirmed IBD diagnosis [b] | 1.97 (1.33-2.91) | 2.21 (1.53-3.20) | 1.12 (0.86-1.46) |
| Analysis excluding pneumococcal infections as opportunistic infections | 2.12 (1.42-3.17) | 2.07 (1.42-3.03) | 0.98 (0.74-1.29) |
| Opportunistic infections, excluding mycobacterial infections | 1.85 (1.15-2.98) | 1.65 (1.06-2.58) | 0.89 (0.66-1.21) |

[a] For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section.[b] Patients with only one single hospital discharge IBD diagnosis and no pharmacy claim for any of the following IBD medications: aminosalicylates, enteral budesonide, thiopurines and anti-TNFs, were considered to have a non-confirmed diagnosis of IBD



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