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

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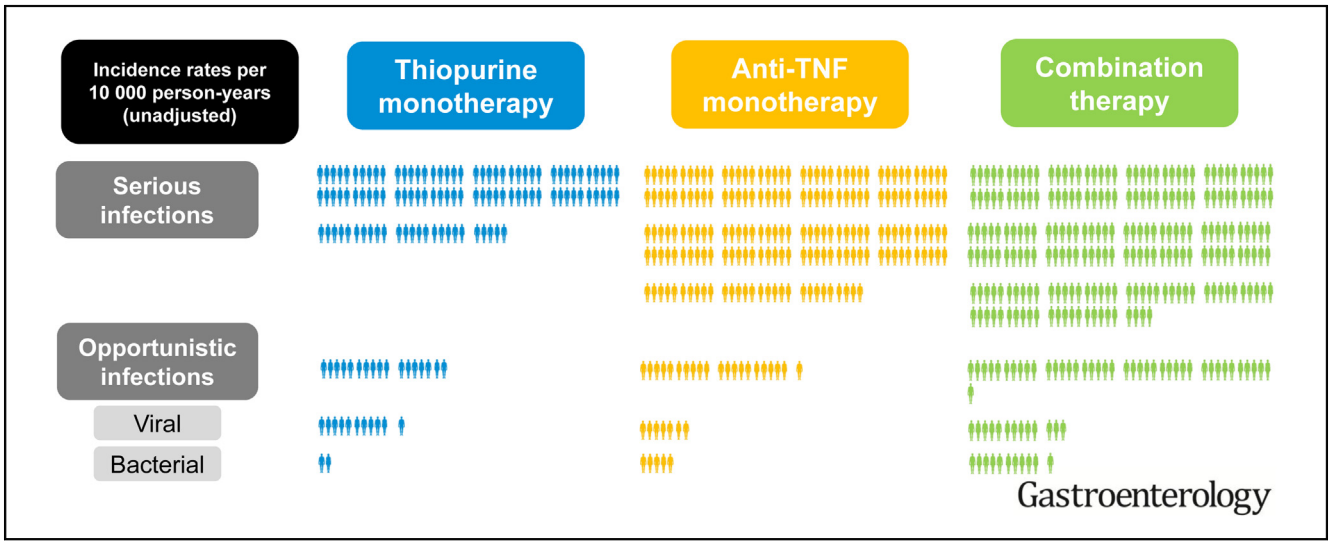

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BACKGROUND & AIMS: The risk of infection associated with tumor necrosis factor antagonists (anti-TNF) and thiopurines (combination therapy) is uncertain. We assessed the risk of serious and opportunistic infections in patients with inflammatory bowel disease (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 sociodemographic 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 with anti-TNF monotherapy, combination therapy was associated with increased risks of serious infection (hazard ratio [HR], 1.23; 95% confidence interval [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 with thiopurine monotherapy (HR, 0.57; 95% CI, 0.38–0.87). **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: Anti-TNFs; Combination Therapy; Infection; Inflammatory Bowel Disease; Thiopurines.

Abbreviations used in this paper: **anti-TNF, tumor necrosis factor antagonists; CI, confidence interval; IBD, inflammatory bowel disease; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th edition; LTD, long-term disease; NMSC, non-melanoma skin cancer; PY, person-year; SD, standard deviation; SNIIRAM, Système National d'Information Inter-Régimes de l'Assurance Maladie.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The risk of infection associated with the combination of anti–tumor necrosis factor agents (anti-TNFs) and thiopurines (combination therapy) is uncertain, and whether this risk is higher with anti-TNFs than with thiopurines is unclear.

NEW FINDINGS

This nationwide cohort study provides evidence of an increased risk of serious infections with anti-TNF monotherapy compared to thiopurine monotherapy and an increased risk of serious and opportunistic infections with combination therapy compared to anti-TNF monotherapy.

LIMITATIONS

Infections were identified based on hospital discharge diagnosis codes.

IMPACT

The risk of serious and opportunistic infections should be taken into consideration and weighed against potential benefits of the various treatment strategies used in IBD management.

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] whereas an increased risk of opportunistic infections has been reported compared with 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.

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. Because of 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 health care professionals and individuals' status with respect to full reimbursement of care for severe long-term diseases (LTDs),[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 (Programme de médicalisation des systèmes d'information, PMSI), 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 pharmacoepidemiologic studies.[16–20]

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

Study Population

The source population included all patients 18 years or older identified with IBD before 2014 from the French administrative health databases. Identification of IBD patients was based on 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 nonconfirmed diagnosis of IBD. We did not include corticosteroids except enteral budesonide in this definition, because they are widely prescribed for conditions other than IBD. For patients with 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 having prevalent cases of IBD, and 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, or 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 those with prevalent cases and the date of IBD diagnosis for those with incident cases. Because IBD therapeutic management may be different after occurrence of cancer and because chemotherapy may lead to 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 to 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 1 month.[22] Patients who received infliximab were considered exposed for 2 months after the infusion; those who received adalimumab or thiopurines were considered exposed for 1 month after 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 1 group of drug exposure. Treatment withdrawal was defined by a period of at least 2 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; musculoskeletal; and other infections (including sepsis, nonclassified opportunistic, and mycobacterial infections). Opportunistic infections were classified according to pathogens. These included viral, mycobacterial, bacterial, fungal, and parasitic infections. Supplementary Tables 1 and 2 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, and comorbidities (based on data from hospitalization discharges, LTDs, and specific procedures or treatments, see details in Supplementary Table 3) including history of cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, diabetes, cirrhosis, obesity, alcohol use disorder, smoking behavior, and 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 every 6 months, respectively. Because 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 3 months.

Statistical Analyses

We used marginal structural Cox proportional hazard models[24] adjusted for the time-fixed and time-varying covariates listed to compare the risks of serious and opportunistic infections associated with exposure to: (1) combination therapy vs anti-TNF monotherapy, (2) combination therapy vs thiopurine monotherapy, and (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. Weight calculations were performed as suggested by Cole and Hernán.[25] Detailed statistical method is provided in the Supplementary Material.

The main analysis was restricted to patients with no history of cancer and a confirmed diagnosis of IBD. Additional analyses included subgroup analyses stratified on age at cohort entry (18–64 years and 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 before the start of follow-up to avoid including potential prevalent infections. Second, because 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, because 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 nonconfirmed IBD diagnosis or a medical history of cancer.

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

Results

Characteristics of the Cohort

Among the 246,704 individuals 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, and 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 (standard deviation [SD], 16.4) years at cohort entry. Half had a diagnosis of Crohn's disease (95,921 [50.3%]) and half ulcerative colitis (94,773 [49.7%]). One third (63,101 [33.1%]) were incident cases, whereas 22.0% (41,878) had been diagnosed for at least 10 years. IBD-related complications had occurred within the 6 months preceding cohort entry in 4.3% (8131). 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;

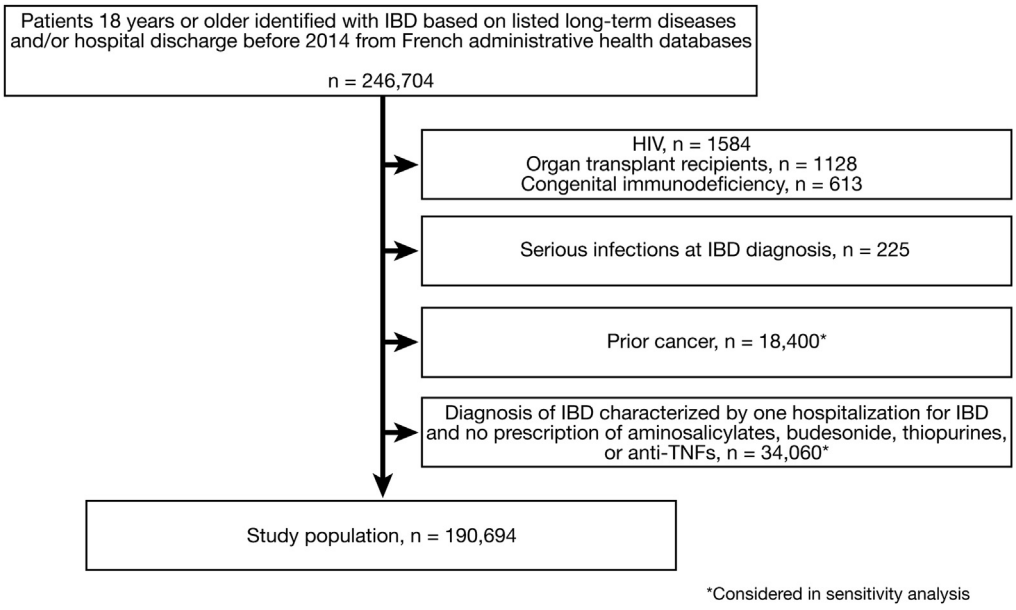

Figure 1. Study population flowchart.

most of them had longstanding, uncomplicated ulcerative colitis. Those exposed to thiopurines and/or anti-TNFs were mostly younger than 40 years, were 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.

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 after 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 5 parasitic infections occurred. Twenty patients with opportunistic infections (3%) died within 3 months after 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 with patients unexposed to thiopurines and anti-TNFs (Supplementary Table 6).

Among exposed patients, combination therapy was associated with an increased risk of serious infections vs anti-TNF monotherapy (hazard ratio [HR], 1.23; 95% confidence interval [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 with 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 with 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 with patients unexposed to thiopurines and anti-TNFs (Supplementary Table 6).

Combination therapy was associated with an increased risk of opportunistic infections compared with 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

Table 1. Patient Characteristics at Cohort Entry According to Subsequent Treatment Exposure During Follow-Up[a]

Characteristics	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, *d*, mean (SD)	—	508 (595)	547 (580)	238 (281)
Age at cohort inclusion, *y*, 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)
Narcotics use,[c] n (%)	25,301 (16.0)	7845 (16.5)	5275 (20.1)	2105 (17.5)

[a]Patients exposed to more than 1 exposure group during follow-up were considered in each corresponding group.
[b]Free access to health care for people with an annual income less than 50% of poverty threshold.
[c]As registered within 6 months before cohort entry (except for IBD disease activity assessment [within 1 year]).

associated with an increased risk of opportunistic infections compared with 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 with 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% CI, 1.15–3.40 and HR, 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 65 years or older compared with younger patients. Specifically, the annual incidence of serious infection in patients 65 years or older and exposed to anti-TNFs, either in monotherapy or combination therapy, was approximately 5% (Table 5). However, HRs 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

Table 2. Incidence of Serious and Opportunistic Infections According to Treatment Exposure During Follow-Up, Overall and by Infection Site and Pathogen

Type of Infection	Unexposed to Thiopurines and Anti-TNFs (719,407 PY)	Exposed to Thiopurine Monotherapy (109,177 PY)	Exposed to Anti-TNF Monotherapy (57,835 PY)	Exposed to Combination Therapy (11,143 PY)
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)

NOTE. Values are n (incidence rates/1000 person-years).
ENT, ear, nose, and throat; GI, gastrointestinal.

serious infections and of mycobacterial and opportunistic bacterial infections are increased with anti-TNF monotherapy compared with thiopurine monotherapy. However, the risk of opportunistic infections with anti-TNF monotherapy does not differ from that of thiopurine monotherapy because of 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 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 with patients not exposed to anti-TNFs after adjustment for thiopurines use,[8] but another cohort study reported no increased risk of serious infections associated with anti-TNF exposure as combination therapy or monotherapy, compared with patients treated with thiopurines.[10] A similar risk of serious infections with combination therapy compared with anti-TNF monotherapy was reported in a cohort study including new anti-TNF users in Medicare.[14] However, patients covered by Medicare are older than 65 years or have chronic diseases; therefore, these findings may be applicable only 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. However, disease activity and corticosteroids are 2 major predictors of infection as shown in a US study based on the TREAT (ie, Crohn's Therapy, Resource, Evaluation and Assessment Tool) registry,[9] and they may have an impact on

Table 3. Multivariable Adjusted HRs (95% CIs)[a] of Serious Infections According to Medication Exposure, Overall and by Infection Site

Type of Infection	Exposed to Combination Therapy vs Anti-TNF Monotherapy	Exposed to Combination Therapy vs Thiopurine Monotherapy	Exposed to Anti-TNF Monotherapy vs 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.

Table 4. Multivariable Adjusted HRs (95% CIs)[a] of Opportunistic Infections According to Medication Exposure, Overall and by Pathogen

Type of Infection	Exposed to Combination Therapy vs Anti-TNF Monotherapy	Exposed to Combination Therapy vs Thiopurine Monotherapy	Exposed to Anti-TNF Monotherapy vs 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.

treatment modification and occurrence of infection. To our knowledge, the present study, based on a large and unselected population, is the first to provide 2-by-2 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 with thiopurine monotherapy. In the recent Danish study, an increased risk of serious infection was reported with anti-TNFs, although it was statistically significant only for skin 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.

Although 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 with 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 with 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, although combination therapy was associated with an increased risk of opportunistic viral infections compared with anti-TNF monotherapy, no difference was found compared with 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 for serious and opportunistic infections.[9,26] After adjustment for major comorbidities and IBD disease activity, relative risks of serious or

Table 5. Incidence of Serious and Opportunistic Infections According to Age Category at Cohort Entry

Type of Infection	Unexposed to Thiopurines and Anti-TNFs 18–64 *y*: 627,683 PY ≥65 *y*: 91,724 PY	Exposed to Thiopurine Monotherapy 18–64 *y*: 102,593 PY ≥65 *y*: 6584 PY	Exposed to Anti-TNF Monotherapy 18–64 *y*: 55,975 PY ≥65 *y*: 1860 PY	Exposed to Combination Therapy 18–64 *y*: 10,905 PY ≥65 *y*: 238 PY
Serious infections, overall				
18–64 *y*	3954 (6.3)	972 (9.5)	996 (17.8)	238 (21.8)
≥65 *y*	2113 (23.0)	177 (26.9)	99 (53.2)	12 (50.5)
Opportunistic infections, overall				
18–64 *y*	231 (0.4)	169 (1.6)	108 (1.9)	44 (4.0)
≥65 *y*	91 (1.0)	18 (2.7)	11 (5.9)	2 (8.4)

NOTE. Numbers are n (incidence rates/1000 PY).

Table 6. Multivariable Adjusted HRs (95% CIs)[a] for any Serious or Opportunistic Infections According to Medication Exposure and Age Category at Cohort Entry

Type of Infection	Exposed to Combination Therapy vs Anti-TNF Monotherapy	Exposed to Combination Therapy vs Thiopurine Monotherapy	Exposed to Anti-TNF Monotherapy vs Thiopurine Monotherapy
Serious infections, overall			
18–64 *y*	1.20 (1.02–1.42)	1.98 (1.68–2.34)	1.65 (1.49–1.83)
≥65 *y*	1.34 (0.64–2.80)	2.30 (1.14–4.65)	1.71 (1.28–2.29)
Opportunistic infections, overall			
18–64 *y*	1.95 (1.30–2.93)	2.02 (1.37–2.96)	1.03 (0.78–1.36)
≥65 *y*	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.

opportunistic infections were of similar magnitude, regardless of age. However, the absolute risks were 2- to 3-fold greater in patients 65 years or older compared with 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 large numbers 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 because their marketing authorizations in inflammatory bowel disease were obtained in November 2014 and 2016, respectively, in France. Patients are unselected because universal access to health care 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 and anti-TNF and thiopurines monotherapies. Finally, we assessed time-dependent confounding variables such as IBD activity and corticosteroid exposure.

Some limitations should be noted. To date, 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 the 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 thiopurines or anti-TNFs compared with unexposed patients reported in our study may also strengthen the external validity of our findings. 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 result 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. Finally, 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 treated with only aminosalicylates, this is unlikely to have biased our results because 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 patients 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.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.04.012.

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Supplementary Material

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 the 1st and 99th 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, because treatment assignment was recorded continuously rather than during scheduled follow-up visits. It may also provide a precise estimation of drug exposure, notably treatment introduction, whereas the increased risk of serious infections associated with anti-TNFs was mostly observed right after treatment introduction.[4] In a complementary analysis, we divided the time scale into discrete periods of 1 month for the estimation of the weights, and results were shown to be consistent.

After truncation at the 1st percentile (0.43) and 99th 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% CIs.

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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

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
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

Supplementary Table 2. Continued

Subgroup of Infection	Diagnoses	ICD-10
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

ENT, ear, nose and throat; GI, gastrointestinal.

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

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)
ENT infections		263 (3.1)
	Mastoiditis	4 (0.0)
	Nasopharyngitis	0
	Sinusitis	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)

Supplementary Table 4. Continued

Subgroup of Infection	Diagnoses	n (%)
Other infections		1369 (16.0)
	Infection of the eye	9 (0.1)
	Infections in the nervous system	13 3 (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)

ENT, ear, nose and throat; GI, gastrointestinal.

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

Supplementary Table 6. Multivariable Adjusted HRs (95% CIs)[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

Type of Infection	Exposed to Combination Therapy vs Unexposed to Thiopurines or Anti-TNFs	Exposed to Anti-TNF Monotherapy vs Unexposed to Thiopurines or Anti-TNFs	Exposed to Thiopurine Monotherapy vs 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)

ENT, ear, nose, and throat; GI, gastrointestinal.
[a]For the predictors for which the multivariable model adjusted, see the Covariates subsection of the Methods section.

Supplementary Table 7. Multivariable Adjusted HRs (95% CI)[a] of Serious and Opportunistic Infections According to Treatment Exposure by IBD Subtype and in Sensitivity Analyses

	Exposed to Combination Therapy vs Anti-TNF Monotherapy	Exposed to Combination Therapy vs Thiopurine Monotherapy	Exposed to Anti-TNF Monotherapy vs 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 before start of follow-up	1.22 (1.03–1.45)	2.13 (1.80–2.52)	1.74 (1.58–1.93)
Analysis not 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 before start of follow-up	1.99 (1.33–2.98)	2.17 (1.47–3.19)	1.09 (0.83–1.44)
Analysis not 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 for which the multivariable model adjusted, see the Covariates subsection of the Methods section.
[b]Patients were considered to have a nonconfirmed diagnosis of IBD if they had only 1 single hospital discharge IBD diagnosis and no pharmacy claim for any of the following IBD medications: aminosalicylates, enteral budesonide, thiopurines, and anti-TNFs.