Impact of anti-tumor necrosis factor agents on the risk of colorectal cancer in patients with ulcerative colitis: nationwide French cohort study Short title: Colorectal cancer and anti-TNF in UC

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Short title: Colorectal cancer and anti-TNF in UC

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Abstract

Background and Aims: Patients with ulcerative colitis (UC) are at increased risk of colorectal cancer. Anti-tumor necrosis factor agents (anti-TNF) aim to reduce chronic colonic inflammation and may lower the risk of colorectal cancer (CRC), but the impact of anti-TNF exposure has not yet been assessed in population-based cohort studies. The aim of this nationwide study was to assess the risk of CRC in patients with UC exposed to anti-TNF.

Methods: Based on the French health insurance database, patients aged 18 years or older with a diagnosis of UC, previously exposed to or initiating immunosuppressive treatment were followed from 1 January 2009 until 31 December 2018. The risk of CRC associated with anti-TNF exposure was assessed using marginal structural Cox proportional hazard models adjusting for baseline and time-varying comorbidities including primary sclerosing cholangitis, UC disease activity, colonoscopic surveillance, and other medications.

Results: Among 32,403 patients with UC, 15,542 (48.0%) were exposed to anti-TNF. During a median follow-up of 6.1 years (198,249 person-years), 246 incident CRC occurred (incidence rate per 1000 person-years, 1.24; 95% CI, 1.10-1.41). While the risk of CRC associated with anti-TNF exposure was not decreased in the overall group of patients with UC (HR, 0.85; 95% CI, 0.58-1.26), anti-TNF exposure was associated with a decreased risk of CRC in patients with long- standing colitis (disease duration ≥ 10 years) (HR, 0.41; 95% CI, 0.20-0.86).

Conclusions: In a nationwide cohort of patients with UC, anti-TNF exposure was associated with a decreased risk of CRC in patients with long-standing colitis.

Keywords: inflammatory bowel disease; ulcerative colitis; colorectal cancer

INTRODUCTION

Ulcerative colitis (UC) is a lifetime inflammatory rectal or colorectal disease characterized by relapsing or continuous colonic inflammation, with young adult onset in most cases. UC is associated with an increased risk of colorectal cancer, and patients with UC, particularly those with longstanding (more than 7-10 years of disease duration) extensive colitis,[1,2] may develop colitis-associated cancers,[3] in addition to sporadic colorectal cancers.[4–6] It is estimated that young adults with pancolitis have a lifetime risk of colorectal cancer that exceeds 15%.[4]

Since the excess of risk is related to colonic chronic inflammation,[7] UC treatments, by decreasing colonic inflammation, may decrease the risk of colorectal cancer. While several population based cohort studies and meta-analyses of observational studies assessed the impact of aminosalicylates and thiopurines on the risk of colorectal cancer,[1,8–11] no population-based cohort study specifically assessed the impact of anti-TNF on this risk. A Danish nationwide cohort study whose aim was to assess the overall risk of cancer in patients with inflammatory bowel disease (IBD) treated with anti-TNF, did not report a chemopreventive effect on the risk of colorectal cancer in subgroup analyses, but these analyses included patients with UC and Crohn's disease (CD), notably patients with ileal CD, without adjusting for colonic disease extent.[12] Finally, an increasing number of patients with UC are exposed for prolonged periods to anti-TNF,[13] and data on the potential chemopreventive effect of anti-TNF on the risk of colorectal cancer are needed to further clarify the benefit-risk balance of anti-TNF.

The aim of this study was to assess the impact of anti-TNF on the risk of colorectal cancer in patients with UC, using data from the French nationwide population-based cohort of patients with UC.

METHODS

Data sources

The population-based cohort study was based on the French National Health Insurance database (*Système national des données de santé [SNDS]*),[14] which covers 95% of the French population. Patients are unselected in the SNDS and all French residents are included because universal access to healthcare is warranted for all French residents. The SNDS contains all drugs reimbursements, outpatient medical and nursing care, which have been prescribed or done by health-care professionals. The SNDS also includes individuals' status with respect to full reimbursement of care for severe long-term diseases (LTDs), including UC, which allows to assess the date of UC diagnosis.[13] Outpatient data are linked to the French national hospital discharge database, which provides individual medical information 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 in IBD.[15,16] Several studies estimated the reliability of the information recorded and the accuracy of their coding in different fields,[14] and the SNDS had been used for research purposes to measure disease incidence and identify determinants of medical conditions, including colorectal cancer.[17] Detailed individual-level information regarding hospitalizations and medical treatment were available from January 1, 2006 and January 1, 2008, respectively.

Study population

The source population included all patients 18 years or older identified with UC based on listed long-term diseases and/or hospital discharge diagnosis (main or related discharge diagnosis) before December 31, 2017 from the French administrative health databases. The risk of colorectal cancer is driven by UC disease severity, while disease activity greatly differs between patients with mild UC never exposed to immunosuppressive treatment or biologics and patients with more severe UC treated with these drugs. In order to reduce confounding by disease severity, only patients exposed to immunosuppressive treatment or biologics including thiopurines, methotrexate, anti-TNF, vedolizumab, ustekinumab, and tofacitinib, were included.

The date of UC diagnosis was defined as the earliest date between the first hospital discharge diagnosis of UC and the date of UC onset as registered for eligibility for full

reimbursement of care. In case of multiple hospitalizations with ICD-10 codes related to both UC and CD, the most recent diagnosis at cohort entry was retained. To avoid potential confounding factors that may increase the risk of colorectal cancer, patients with a history of any cancer (including colorectal cancer but excluding non melanoma skin cancer) were excluded. Likewise, patients with a history of colectomy were excluded as these patients were no longer at risk of colorectal cancer (based on data from hospitalization discharges, LTDs and specific procedures; see details in Supplementary Table 1).

The date of cohort entry was January 1, 2009 for patients previously exposed to immunosuppressive treatment or biologics and was the date of immunosuppressive treatment or biologics initiation for patients who were naïve to immunosuppressive treatment or biologics before January 1, 2009. Patients were followed until December 31, 2018, death, loss to follow up, colectomy, colorectal cancer, whichever occurred first. In case of loss to follow-up, the end of follow up was the last known contact date, defined as the last claim in the database.

Drug exposure

Exposure to anti-TNF (infliximab, adalimumab, and golimumab) was assessed during follow-up. First day of treatment exposure was defined as the day of first infliximab infusion or treatment delivery. Patients who received infliximab were considered exposed for two months following each infusion; those who received adalimumab or golimumab were considered exposed for one month following each delivery. A 3-month lag period from cohort entry was considered to avoid including incipient cancers (unlikely to be caused by recent treatment modification). During this 3-month lag period, exposed patients did not contribute person-time to the user group but were categorized as unexposed in order to prevent immortal time bias. Similarly, exposure time during follow-up started 3 months after anti-TNF initiation and was extended 3 months after treatment switch or withdrawal.

Study outcome

The main outcome was the occurrence of incident colorectal cancer as defined by an algorithm previously validated within the SNDS to identify incident cancers,[17] and restricted to incident colorectal cancer. This algorithm is based on full reimbursement of care for colorectal cancer, hospitalization with a primary diagnosis of colorectal

cancer, or occurrence of chemotherapy or radiotherapy associated with a diagnosis of colorectal cancer (related ICD-10 codes C18, C19, or C20).

Covariates

Two groups of covariates were considered. Time-fixed covariates were evaluated at cohort entry and included age, sex, complementary universal health insurance coverage, disease duration, UC related endoscopy and imaging in preceding year, previous exposure to aminosalicylates, methotrexate, thiopurines, and anti-TNF, primary sclerosing cholangitis (PSC) and comorbidities (based on data from hospitalization discharges, LTDs, and specific procedures or treatments, see Supplementary Table 1) including history of cardiovascular disease, cerebrovascular disease, atherosclerosis, chronic pulmonary disease, chronic kidney disease, rheumatic disease, cirrhosis, venous thromboembolism, history of serious infections, and traditional cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes mellitus, obesity, tobacco smoking, and alcohol use disorders).[18] Since there is no specific ICD-10 code for PSC, PSC diagnosis was based on four parameters: (1) hospital discharge diagnosis code related to cholangitis; (2) LTDs related to cholangitis; (3) initiation of ursodeoxycholic acid; (4) occurrence of a liver biopsy. PSC diagnosis was validated in presence of at least two of these four parameters, and the date of PSC diagnosis was the date of the occurrence of the second parameter. Disease extent according to Montreal classification was based on ICD-10 codes, and was defined as unspecified in case of UC related diagnosis codes without precision on disease extent.[19] Time-varying covariates included UC disease severity assessed every six months during follow-up, based on exposure to aminosalicylates, methotrexate, and thiopurines, and occurrence of UC related hospitalization. The occurrence of colonoscopy was updated every year. See Supplementary Table 1 for related ICD-10 codes and procedure codes.

Statistical analysis

Marginal structural Cox proportional hazard models adjusted for the time-fixed and time-dependent covariates were used to estimate the risk of colorectal cancer associated with exposure to anti-TNF. Age and UC disease duration were included as continuous covariates in the model. Marginal structural models are used in case of time-dependent covariates (such as exposure to aminosalicylates, methotrexate or thiopurines, and UC

disease activity) that might be associated with both exposure and outcomes [20] (time-dependent confounders) and could also be affected by past exposure to anti-TNF. Weight calculations were performed as suggested by Cole and Hernán.[21] Details of the applied statistical method are provided in the supplementary appendix.

Additional prespecified analyses included subgroups analyses stratified on gender, age at cohort entry (18-49; ≥ 50 years), and UC disease duration (0-9; ≥ 10 years) to assess the impact of anti-TNF exposure in patients with longstanding UC. We performed several sensitivity analyses to test the robustness of our results. First, we excluded patients exposed to vedolizumab, ustekinumab, or tofacitinib before cohort entry and follow-up was censored at vedolizumab, ustekinumab, or tofacitinib introduction. Second, patients with a concomitant diagnosis of PSC were excluded. Third, we only included incident users of immunosuppressive treatment and anti-TNF. Fourth, since disease extent changes over time, we considered disease extent as a time-varying covariate assessed every three months during follow-up. Lastly, we performed sensitivity analyses restricted to patients with a specified colonic extent.

The statistical analyses were performed using SAS (version 9.4) statistical software (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of the cohort

Among the 34 976 patients 18 years or older identified with UC before 2017 and exposed to immunosuppressive treatment or biologics, we excluded 1442 patients with a prior medical history of cancer, and 1131 patients who underwent colectomy before cohort entry. We included a total of 32 403 patients in the main analysis (Figure 1). During a total follow-up of 198 249 person-years, 15 542 (48.0%) patients were exposed to anti-TNF. The median follow-up was of 6.1 (interquartile range [IQR] 3.3-9.7) years. Overall, patients were predominantly male (51.7%), with a median age of 42 (IQR 31-55) years. Incident cases of UC after January 1, 2009 accounted for 48.3% of the cohort, while 16.1% had a disease duration of 10 years or more at cohort entry. The extent of UC was unspecified in 23 516 patients (72.6%). PSC was diagnosed in 270 (0.8%) patients. Patients unexposed to anti-TNF during follow-up had a median age of 43 (IQR 31-55) years and 4497 patients (16.4%) had a disease duration of 10 years or more. Patients exposed to anti-TNF during follow-up had a median age of 390 (IQR 29-51) years and 2060 patients (13.3%) had a disease duration of 10 years or more. Characteristics according to anti-TNF exposure during follow-up are provided in Table 1.

Risk of colorectal cancer

Overall, 246 incident cases of colorectal cancer occurred during follow-up. Patients diagnosed with colorectal cancer were mainly male (63.8%) and had a median age of 54 (IQR 40-65) years at cohort entry (Supplementary Table 2). Among patients with colorectal cancer, 10 (4.1%) were diagnosed with PSC. Median age at diagnosis of colorectal cancer was 60 years (IQR 49-72) and 53 years (IQR 36-65) in patients unexposed and exposed to anti-TNF, respectively.

The overall incidence rate of colorectal cancer was 1.24 (95% CI, 1.10-1.41) per 1000 person-years (PY). The incidence rate was higher in men compared with women (IR per 1000 PY, 1.54 [95% CI, 1.31-1.80] and 0.93 [95% CI, 0.75-1.14] in men and women, respectively). The incidence rate was 2.60 (95% CI, 2.12-3.20) per 1000 PY in patients with a disease duration of 10 years or more compared to 0.95 (95% CI, 0.81-1.12) per 1000 PY in patients with a disease duration of less than 10 years at cohort entry. Incidence rates according to treatment exposure are provided in Table 2.

In the overall cohort of patients with UC, the risk of colorectal cancer did not differ between patients exposed to anti-TNF and those unexposed with a hazard ratio [HR] of 0.85 (95% CI, 0.58-1.26) (Figure 2).

The absence of impact of anti-TNF exposure was consistent in men (HR 0.72, 95% CI 0.42-1.21) and women (HR 0.99, 95% CI 0.55-1.76), as well as in patients aged 18 to 49 years at cohort entry (HR 0.83, 95%CI 0.48-1.42) and patients older than 50 years at cohort entry (HR 0.91, 95% CI 0.53-1.58). Regarding disease duration, exposure to anti-TNF was associated with a decreased risk of colorectal cancer in patients with a disease duration of 10 years or more (HR 0.41, 95% CI 0.20-0.86), while this effect was not observed in patients with a disease duration of less than 10 years (HR 1.11, 95% CI 0.71-1.75).

In preplanned sensitivity analyses (Supplementary Table 3), results remained unchanged after exclusion of patients exposed to vedolizumab, ustekinumab, or tofacitinib before cohort entry and follow-up censoring at vedolizumab, ustekinumab, or tofacitinib introduction (HR 0.87, 95%CI 0.59-1.27), exclusion of prevalent users (HR 0.99, 95% CI 0.58-1.69), exclusion of patients with PSC (HR 0.83, 95% CI 0.57-1.21), or after considering disease extent as time-dependent covariate (HR 0.71, 95%CI 0.47-1.08). Exclusion of patients with unspecified colonic extent did not modify the results (HR 1.01, 95% CI 0.41-2.44). The protective effect associated with anti-TNF exposure observed in patients with longstanding colitis remained after excluding patients with unspecified colonic extent (HR 0.22, 95% CI 0.06-0.79).

DISCUSSION

Based on a nationwide cohort of patients with UC, our findings suggest that exposure to anti-TNF agents is associated with a decreased risk of colorectal cancer in patients with longstanding colitis, after adjustment for medication, disease activity, and colonoscopic surveillance.

There are very few data on the risk of colorectal cancer associated with anti-TNF exposure. A recent Danish cohort study assessing the impact of anti-TNF on the overall risk of cancer in IBD,[12] reported no decreased risk of colorectal cancer associated with anti-TNF exposure, although this analysis was a subgroup analysis including patients with ileal CD and based on a small number of exposed cases (8 patients exposed to anti-TNF developed colorectal cancer). Due to the small number of patients with colorectal cancer in this study, no additional subgroup analyses were available, whereas the risk of colorectal cancer greatly differs according to age and disease duration.[22] The sample size of our cohort allowed us to assess the impact of anti-TNF in these subgroups. Until now, no other study had been able to assess in detail the impact of anti-TNF on the incidence of colorectal cancer in patients with UC according to age, sex, and disease duration.

While we reported no differences in the overall population of patients with UC, anti-TNF exposure was associated with a protective effect on the risk of colorectal cancer in patients with longstanding colitis. Patients with longstanding colitis are the subset of patients with the highest risk of colorectal cancer, as reported in our study and in the CESAME cohort.[1] Colitis-associated cancer mainly occurs in this population, which provides insights on the underlying mechanisms of the risk reduction associated with anti-TNF exposure. Anti-TNF agents are known to induce and maintain clinical remission and mucosal healing,[23] which may explain the chemopreventive effect by reducing chronic colonic inflammation. Colorectal cancer occurrence in patients with a shorter disease duration might be related to sporadic colorectal cancer, which may explain the absence of chemopreventive effect in this subset of patients. Similar findings with thiopurines exposure were reported in the CESAME cohort and in a recent meta-analysis.[1,11]

This study had some limitations that need to be discussed. First, to date, there has been no validation study of the ICD-10 codes related to colorectal cancer in UC in the SNDS database. However, we used an algorithm established in a previous study to identify

colorectal cancer from the SNDS databases with good accuracy compared with cancer registries.[17] The colorectal cancer incidence rates reported in this study are also of similar magnitude compared to previous studies in patients with UC (1.24 per 1000 PY in this study, 1.02 per 1000 PY for patients with UC in the CESAME cohort).[1] The colonic extent was unspecified in the majority of patients, since the assessment of disease extent is not mandatory in the hospital discharge summary. However, the protective effect associated with anti-TNF exposure in patients with a disease duration of 10 years or more was observed after restricting the analysis to patients with specified colonic extent. Similarly, we did not include patients with CD since the assessment of disease extent based in ICD-10 codes may be missing and the inclusion of patients with CD might lead to the inclusion of patients without any colonic disease extent. Although the risk of colorectal cancer appears to be the same in UC and CD after adjustment for disease duration and extent of colitis,[4] further studies are required to assess the impact of anti-TNF on the risk of colorectal cancer in patients with CD. It is also noteworthy that the inclusion of prevalent users of anti-TNF in the main analysis (to ensure sufficient statistical power to assess the risk of colorectal cancer) may have caused a prevalent user bias. However, similar results were obtained in the analysis restricted to incident users, suggesting that such a bias, if any, is limited. Lastly, assessment of histological and endoscopic disease activity are not available in the SNDS database. Since patients exposed to anti-TNF tend to have a more severe disease compared to unexposed patients, a potential bias related to residual confounding by disease severity may tend to underestimate the risk reduction of colorectal cancer associated with anti-TNF, suggesting that such a bias, if any, did not alter the association between anti-TNF and the protective effect observed. Environmental factors such as red meat consumption are also not assessed in the SNDS database. We adjusted for traditional cardiovascular risk factors, which may be surrogate markers of metabolic syndrome. Further studies are required to assess the impact of nutrition on the risk of colorectal cancer in patients with UC.

This study has several strengths. The primary strength is its nationwide, population-based cohort design. The database is comprehensive in that it includes all medical prescriptions and hospital stays for UC in France. Besides, this cohort has been previously described and reported treatment exposure, hospitalization, and incidence similar to those reported in the literature.[13] Patients with UC treated with anti-TNF are predominantly patients with an extensive disease.[24] To reduce this potential

confounding bias, as well as residual confounding by disease severity, we only included patients treated with immunosuppressive treatment or biologics. Aside from reducing the likelihood of confounding, this design also addressed the clinically relevant question of the impact of anti-TNF regarding the risk of colorectal cancer for patients requiring immunosuppressive treatment or biologics. We used a statistical method that took into account time-dependent exposure and confounding variables such as UC disease activity, exposure to aminosalicylates, methotrexate, or thiopurines to properly assess the individual effect of anti-TNF. The long follow-up allowed us to adjust for the occurrence of colonoscopy during follow-up, which may impact the detection of colorectal cancer.

CONCLUSION

In conclusion, this nationwide population-based cohort study including more than 30 000 patients is the first to specifically assess the impact of anti-TNF agents on the risk of colorectal cancer in patients with UC. Our study provides significant evidence that anti-TNF exposure is associated with a decreased risk of colorectal cancer in patients with longstanding UC. These findings may contribute to assess more accurately the benefit-risk balance of anti-TNF exposure in UC, notably in patients with longstanding colitis.

Figure Legends:

Figure 1. Study population flowchart

Figure 2. Hazard ratios for colorectal cancer associated with anti-TNF exposure according to sex, age, and disease duration

Data Availability Statement:

The data underlying this article are available in the article and in its online supplementary material

Contributors:

Concept and design: Beaugerie, Charkaoui, Kirchgesner. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Charkaoui. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Kirchgesner. Supervision: Kirchgesner.

Conflict of Interest Disclosures:

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

Characteristics	Unexposed to anti-TNFs (n=27 441)	Exposed to anti-TNFs (n=15 542)	Total (n=32 403)
Age at cohort inclusion, median (IQR)	43 (31-55)	39 (29-51)	42 (31-55)
Male sex, n (%)	14 085 (51.3)	7879 (50.7)	16 756 (51.7)
Complementary universal health insurance, n (%) [b]	2499 (9.1)	1564 (10.1)	2988 (9.2)
Maximum extent of disease according to Montreal classification, n (%)			
E1 (ulcerative proctitis)	1860 (6.8)	1118 (7.2)	2240 (6.9)
E2 (left-sided UC)	3119 (11.4)	1874 (12.1)	3732 (11.5)
E3 (extensive UC)	2256 (8.2)	1721 (11.1)	2915 (9.0)
EX (extent unspecified)	20 206 (73.6)	10 829 (69.7)	23 516 (72.6)
Disease duration at cohort entry, median (IQR)	2.7 (0.6-7.2)	2.0 (0.5-5.8)	2.5 (0.6-7.0)
UC assessment, n (%) [c]			
Lower GI endoscopy	16 985 (61.9)	11 078 (71.3)	20 754 (64.0)
Radiology tests	6100 (22.2)	4385 (28.2)	7741 (23.9)
Inflammatory bowel disease drugs, n (%)			
Aminosalicylates	23 113 (84.2)	13 565 (87.3)	27 415 (84.6)
Methotrexate	2578 (9.4)	1047 (6.7)	2829 (8.7)
Thiopurines	22 395 (81.6)	9293 (59.8)	24 268 (74.9)
Anti-TNF	3524 (12.8)	6549 (42.1)	6921 (21.4)
Complications related to UC before cohort entry [c]			
Hospitalization related to UC >24 hours	4066 (14.8)	3360 (21.6)	5392 (16.6)
Comorbidities, n (%)			
Cardiovascular disease	2249 (8.2)	1108 (7.1)	2622 (8.1)
Peripheral artery disease	478 (1.7)	237 (1.5)	566 (1.7)
Cerebrovascular disease	401 (1.5)	191 (1.2)	473 (1.5)
Chronic kidney disease	294 (1.1)	102 (0.7)	330 (1.0)
Chronic pulmonary disease	5026 (18.3)	2961 (19.1)	6072 (18.7)
Chronic liver disease	204 (0.7)	99 (0.6)	229 (0.7)
Primary sclerosing cholangitis	231 (0.8)	122 (0.8)	270 (0.8)
Rheumatic disease	2082 (7.6)	1739 (11.2)	2825 (8.7)
Serious infections	1103 (4.0)	683 (4.4)	1320 (4.1)
Venous thromboembolism	487 (1.8)	283 (1.8)	592 (1.8)
Diabetes	2052 (7.5)	975 (6.3)	2373 (7.3)
Dyslipidemia	4210 (15.3)	2004 (12.9)	4870 (15.0)
Hypertension	6414 (23.4)	3187 (20.5)	7493 (23.1)
Obesity	1142 (4.2)	686 (4.4)	1416 (4.4)
Smoking behavior	1479 (5.4)	993 (6.4)	1847 (5.7)
Alcohol use disorder	327 (1.2)	202 (1.3)	406 (1.3)

[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 one year for UC assessment and six months for hospitalization related to UC

Table 2. Incidence of colorectal cancer according to medication exposure

	Total 198 249 PY		Unexposed to anti-TNF 143 341 PY		Exposed to anti-TNF 54 908 PY	
	Events	IR [a] (95% CI)	Events	IR [a] (95% CI)	Events	IR [a] (95% CI)
Overall	246	1.24 (1.10-1.41)	189	1.32 (1.14-1.52)	57	1.04 (0.80-1.35)
Sex						
Male	157	1.54 (1.31-1.80)	120	1.63 (1.36-1.95)	37	1.30 (0.94-1.79)
Female	89	0.93 (0.75-1.14)	69	0.99 (0.78-1.25)	20	0.76 (0.49-1.17)
Age at cohort entry						
18-49 years	101	0.77 (0.63-0.93)	71	0.78 (0.62-0.98)	30	0.75 (0.52-1.07)
≥ 50 years	145	2.17 (1.85-2.56)	118	2.27 (1.90-2.72)	27	1.82 (1.25-2.65)
Disease duration						
0-9 years	156	0.95 (0.81-1.12)	111	0.95 (0.79-1.15)	45	0.95 (0.71-1.27)
≥ 10 years	90	2.60 (2.12-3.20)	78	2.89 (2.32-3.61)	12	1.58 (0.90-2.78)

Abbreviation: PY, person-years. [a] Incidence rates per 1000 person-years

Figure 1. Study population flowchart

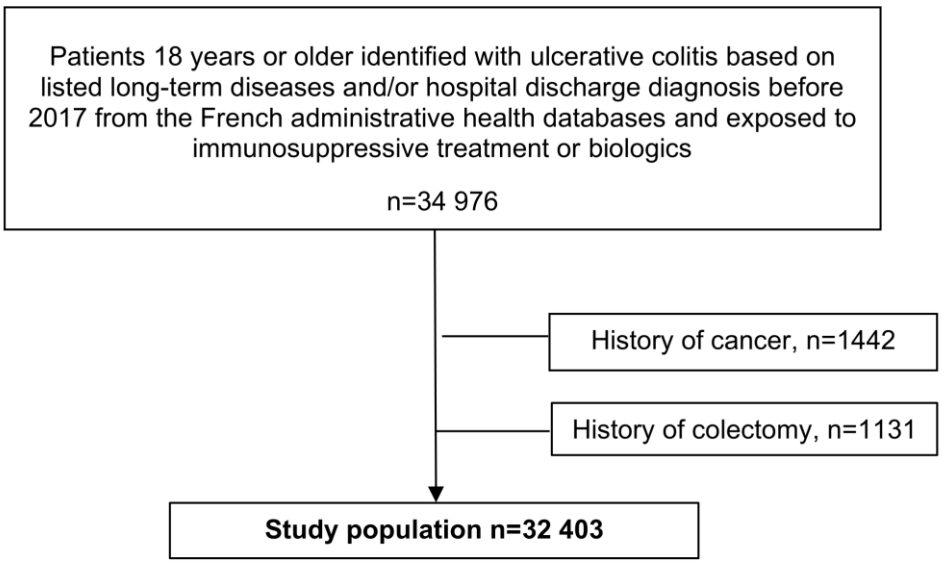
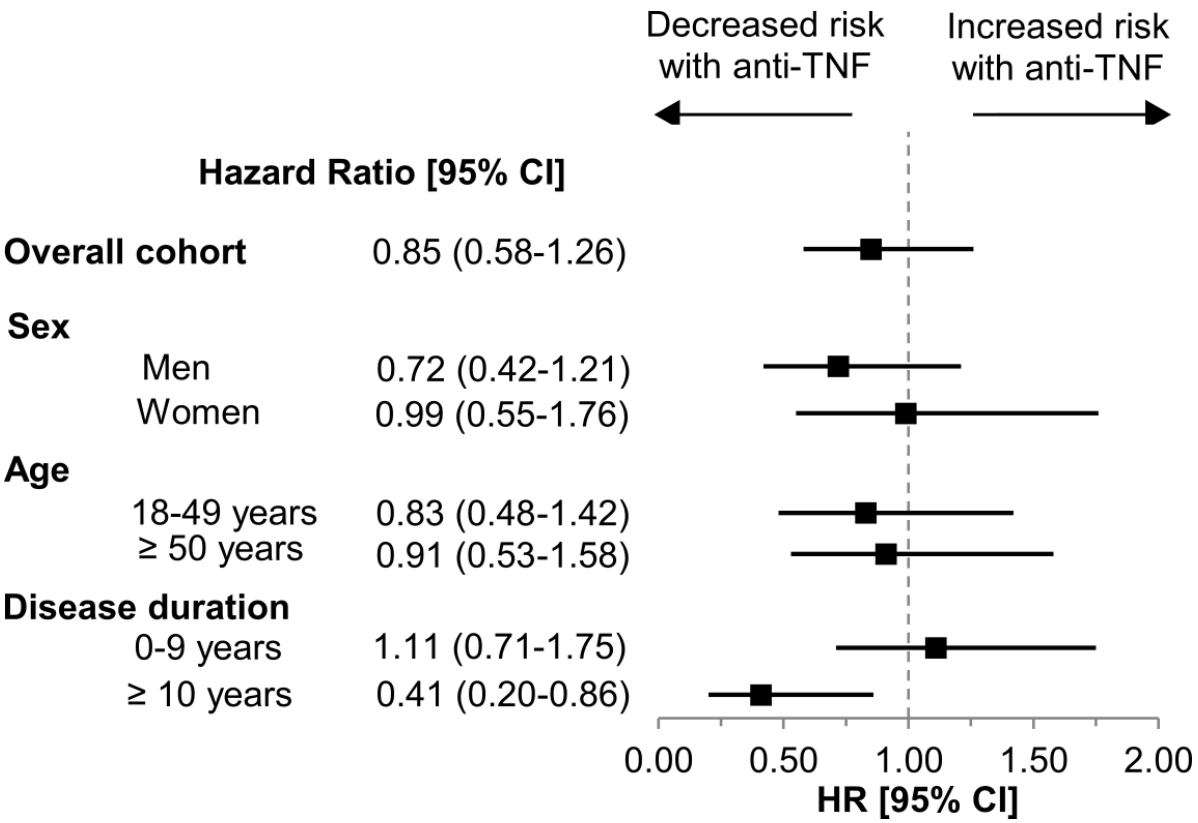


Figure 2. Hazard ratios for colorectal cancer associated with anti-TNF exposure according to sex, age, and disease duration



SUPPLEMENTARY MATERIAL

Supplementary Table 1. Codes used to define exclusion criteria and covariates

Supplementary Table 2: Patients characteristics at cohort entry according to the occurrence of colorectal cancer during follow up

Supplementary Table 3. Multivariable Adjusted hazard ratios of colorectal cancer between anti-TNF exposed and non-exposed patients in sensitivity analyses

Supplementary Figure 1 – Graphical depiction of study follow-up design; (A) patients exposed to immunosuppressive treatment or biologics before January 1, 2009; (B) patients naïve to immunosuppressive treatment or biologics before January 1, 2009 and who started immunosuppressive treatment or biologics after January 1, 2009

Supplemental Appendix: Methods

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	C0-C9, E88.3, G53.3, G55.0, G63.1, G73.2, G94.1, J70.0, J70.1, K52.0, K62.7, L58.0, L58.1, L59.8, D63.0, L59.9, M36.0, M36.1, M90.6, M90.7, M96.2, M96.5, N30.4, O35.6, Z08, Z51.1, Z54.2, Z85	-	Chemotherapy and radiotherapy
Colectomy	-	-	HHFA002, HHFA004, HHFA005, HHFA006, HHFA008, HHFA009, HHFA010, HHFA014, HHFA017, HHFA018, HHFA021, HHFA022, HHFA023, HHFA024, HHFA026, HHFA028, HHFA029, HHFA030, HHFA031
Covariates		-	-
Disease extent according to Montreal classification			
E1 (ulcerative proctitis)	K51.2	-	-
E2 (left-sided UC)	K51.3; K51.5	-	-
E3 (extensive UC)	K51.0	-	-
EX (extent unspecified)	K51.4; K51.8; K51.9	-	-
Primary sclerosing cholangitis	K83.0	A05AA02	Liver biopsy
Chronic liver disease	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;	-	-
Respiratory chronic disease	J40-J44, J47, J96.1	R03AC, R03B	-
Chronic kidney disease	I12, N18, N19, Z49, I13.0, I13.1, Y84.1	-	-
Venus thromboembolism	I26, I80-I82, O22.3, O22.9, O87.1, O88.2	-	-
Rheumatic disease	M05-M09, M45, M35.1, M35.3		
Serious infections	A00-A99 (except A30, A50, A57-A59, A63-A64, A70-74, A97); B00-B99 (except B03-B04, B07, B16, B18-B19, B20-B24, B85-B94, B98) ; G01-G07 (except G03) ;H00-H01, H03.0-H03.1; H06.1; H10.5; H10.8; H13.1; H19.1-H19.2; J01-J06, J10-J18, J20-J22, J36; J39.0-J39.1, J85-J86; K11.3, K12.2, K23.0, K23.80, K67.3, K75.0, K80.0, K80.3, K80.4, K81.0; K83.0, K87.00, K93.0, K93.820; L00-L01, L04-L05, L08, L30.3; M00-M01, M49.0, M60.0, M72.6, M86, M90.0; N10, N30.0, N33.0, N39.0, N41.0, N41.2-N41.3, N45, N70.0, N71.0, N72, N73.3, N74.0-N74.1, N77.1; R57.2; R65.0-R65.1; T82.6-T82.7; T84.5-T84.7; T85.7; U04	-	
Diabetes	E10-E14, M14.2 , M14.6, N08.3, H28.0, H36.0, G59.0, G63.2, G73.0, G99.0, I79.2	A10	-

Supplementary Table 1. Codes used to define exclusion criteria and covariates (continued)				
	Dyslipidemia	E78.0-E78.5	C10	-
	Alcohol use disorder	E244, F100, F101, F10.20-F10.26, F10.3-F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, O35.4, T51, X45, X65, Y15, Z50.2	-	-
	Hypertension	I10-I13, I15	C02 C03 C07 C08 C09	-
	Smoking behavior	F17, Z71.6, Z72.0, T65.2	-	-
	Obesity	E66	-	-

Supplementary Table 2. Patients characteristics at cohort entry according to the occurrence of colorectal cancer during follow up

Characteristics	Colorectal cancer during follow-up (n=246)	No colorectal cancer during follow-up (n=32 157)	Total (n=32 403)
Age at cohort inclusion, median (IQR)	54 (40-65)	42 (31-54)	42 (31-55)
Male sex, n (%)	157 (63.8)	16599 (51.6)	16756 (51.7)
Complementary universal health insurance, n (%) [a]	13 (5.3)	2975 (9.3)	2988 (9.2)
Maximum extent of disease according to Montreal classification, n (%)			
E1 (ulcerative proctitis)	13 (5.3)	2227 (6.9)	2240 (6.9)
E2 (left-sided UC)	23 (9.3)	3709 (11.5)	3732 (11.5)
E3 (extensive UC)	20 (8.1)	2895 (9.0)	2915 (9.0)
EX (extent unspecified)	190 (77.2)	23326 (72.5)	23516 (72.6)
Disease duration at cohort entry, median (IQR)	7.3 (2.0-12.8)	2.5 (0.6-7.0)	2.5 (0.6-7.0)
UC assessment, n (%) [b]			
Lower GI endoscopy	134 (54.5)	20620 (64.1)	20754 (64.0)
Radiology tests	56 (22.8)	7685 (23.9)	7741 (23.9)
Inflammatory bowel disease drugs, n (%)			
Aminosalicylates	197 (80.1)	27218 (84.6)	27415 (84.6)
Methotrexate	20 (8.1)	2809 (8.7)	2829 (8.7)
Thiopurines	200 (81.3)	24068 (74.8)	24268 (74.9)
Anti-TNF	39 (15.9)	6882 (21.4)	6921 (21.4)
Complications related to UC before cohort entry [b]			
Hospitalization related to UC >24 hours	34 (13.8)	5358 (16.7)	5392 (16.6)
Comorbidities, n (%)			
Cardiovascular disease	30 (12.2)	2592 (8.1)	2622 (8.1)
Peripheral artery disease	6 (2.4)	560 (1.7)	566 (1.7)
Cerebrovascular disease	8 (3.3)	465 (1.4)	473 (1.5)
Chronic kidney disease	5 (2.0)	325 (1.0)	330 (1.0)
Chronic pulmonary disease	39 (15.9)	6033 (18.8)	6072 (18.7)
Chronic liver disease	7 (2.8)	222 (0.7)	229 (0.7)
Primary sclerosing cholangitis	10 (4.1)	260 (0.8)	270 (0.8)
Rheumatic disease	17 (6.9)	2808 (8.7)	2825 (8.7)
Serious infections	10 (4.1)	1310 (4.1)	1320 (4.1)
Venous thromboembolism	10 (4.1)	582 (1.8)	592 (1.8)
Diabetes	34 (13.8)	2339 (7.3)	2373 (7.3)
Dyslipidemia	59 (24.0)	4811 (15.0)	4870 (15.0)
Hypertension	83 (33.7)	7410 (23.0)	7493 (23.1)
Obesity	17 (6.9)	1399 (4.4)	1416 (4.4)
Smoking behavior	2 (0.8)	1845 (5.7)	1847 (5.7)
Alcohol use disorder	2 (0.8)	404 (1.3)	406 (1.3)

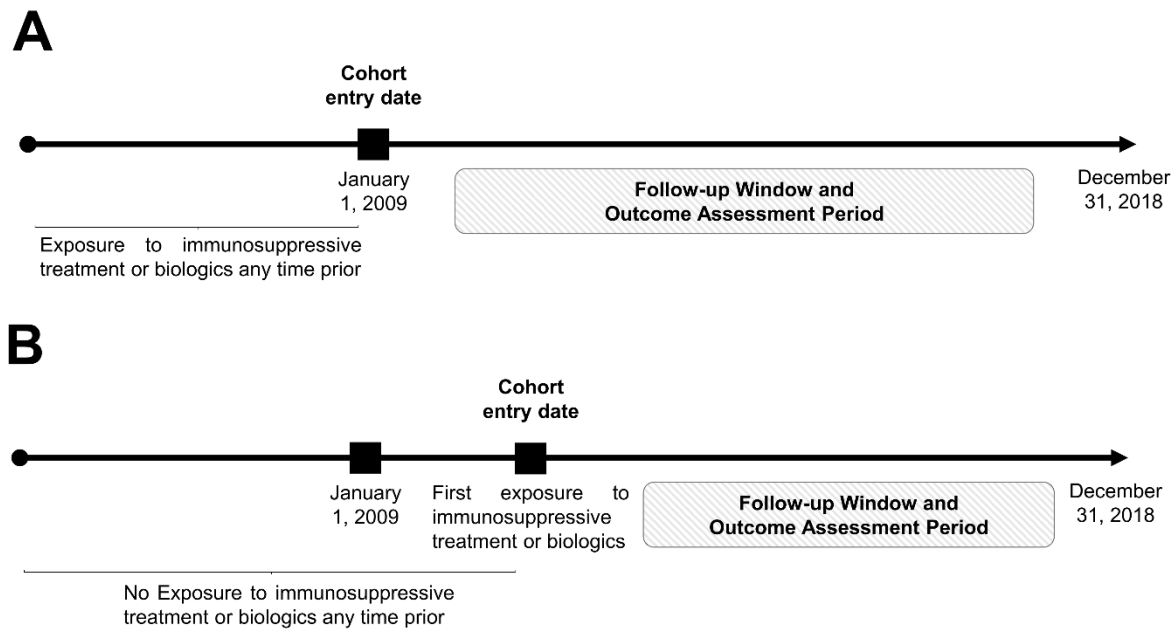
[a] Free access to healthcare for people with an annual income <50% of poverty threshold. [b] As registered within one year for UC assessment and six months for hospitalization related to UC

Supplementary Table 3. Multivariable Adjusted hazard ratios of colorectal cancer between anti-TNF exposed and non-exposed patients in sensitivity analyses [a]

	Exposed to anti-TNF versus unexposed to anti-TNFs
	HR (95% CI)
Main analysis	0.85 (0.58-1.26)
Analysis excluding prevalent users	0.99 (0.58-1.69)
Exclusion of patients exposed to vedolizumab, ustekinumab, or tofacitinib before cohort entry and follow-up censoring at vedolizumab, ustekinumab, or tofacitinib introduction	0.87 (0.59-1.27)
Analysis excluding patients with primary sclerosing cholangitis	0.83 (0.57-1.21)
Analysis considering disease extent as time-dependent covariate	0.71 (0.47-1.08)
Analysis excluding patients with unspecified colonic extent	1.01 (0.41-2.44)
Analysis excluding patients with unspecified colonic extent and restricted to patients with longstanding colitis	0.22 (0.06-0.79)

Abbreviation: HR, hazard ratio. [a] For the predictors the multivariable model adjusted for, see the Covariates subsection of the Methods section.

Supplementary Figure 1 – Graphical depiction of study follow-up design; (A) patients exposed to immunosuppressive treatment or biologics before January 1, 2009; (B) patients naïve to immunosuppressive treatment or biologics before January 1, 2009 and who started immunosuppressive treatment or biologics after January 1, 2009



Supplemental Appendix: Methods

We used marginal structural models to estimate causal effects of anti-TNF on the risk of colorectal cancer.(1) These models adjust for time-dependent covariates with inverse probability treatment weights and are appropriate in the presence of time-dependent covariates (such as exposure to aminosalicylates, methotrexate, or thiopurines and UC disease activity) that might be associated with both anti-TNF exposure and outcomes (time-dependent confounders), but could also be affected by past exposure to anti-TNF. The conditional probability of receiving observed treatment was estimated using binomial logistic regression. Covariates included were the baseline and time-dependent covariates 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 account for selective 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 treatment modification. After calculation, the weights have been truncated at 5^{th} and 95^{th} percentiles to minimize the impact of extreme weights and improve precision.(1,2) We obtained a mean stabilized weight of 1.27 (Standard Deviation 0.77).

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

References:

1. Hernan MÁ, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 2000;11:561–570.
2. Cole SR, Hernán MA. Constructing Inverse Probability Weights for Marginal Structural Models. Am. J. Epidemiol. 2008;168:656–664.