Impact of thiopurines and tumour necrosis factor antagonists on primary sclerosing cholangitis outcomes in patients with inflammatory bowel disease

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Short title: Impact of immunosuppressants in PSC-IBD

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Abbreviations used in this paper:

ATC, Anatomical Therapeutic Chemical;

CCAM, Classification Commune des Actes Médicaux;

CI, confidence interval;

HR, hazard ratio;

IBD, inflammatory bowel disease;

ICD-10, international classification of diseases, 10th edition;

LTD, long-term disease;

PSC, primary sclerosing cholangitis;

PSC-IBD, primary sclerosing cholangitis and inflammatory bowel disease;

SD, standard deviation;

SNDS, Système National des Données de Santé;

TNF, tumor necrosis factor;

Tumor necrosis factor antagonists, anti-TNF;

UDCA, ursodeoxycholic acid;

SUMMARY

Background: Patients with primary sclerosing cholangitis (PSC) and inflammatory bowel disease (IBD) are at risk of biliary tract cancer and liver damage (possibly leading to liver transplantation), and are often treated for IBD with thiopurines and/or tumour necrosis factor antagonists (anti-TNF) on a long-term basis.

Aims: To assess the risk of biliary tract cancer and liver transplantation in patients exposed to thiopurines and/or anti-TNF in a French nationwide cohort.

Methods: We performed a population- based study of patients aged 18 years or older with PSC and IBD in the French national health insurance database. Patients were followed from 1 January 2009 to 31 December 2018. The risks of biliary tract cancer and liver transplantation associated with thiopurines and anti-TNF exposure were assessed with marginal structural Cox proportional hazard models, adjusting for baseline demographics and comorbidities, and time-varying medications and PSC activity.

Results: Among the 1929 patients with PSC and IBD included, 37 biliary tract cancers and 83 liver transplantations occurred. Compared with patients not exposed to thiopurines or anti-TNF agents, patients exposed to thiopurines (hazard ratio [HR], 1.05; 95% confidence interval [CI], 0.39–2.82) or anti-TNF agents (HR, 0.59; 95% CI, 0.13–2.80) had no excess risk of biliary tract cancer. Similarly, patients exposed to thiopurines (HR, 0.67; 95% CI, 0.30–1.48) or anti-TNF agents (HR, 0.68; CI, 0.22–2.09) had no excess risk of liver transplantation.

Conclusions: Patients with PSC and IBD who are exposed to thiopurines or anti-TNF agents are not at excess risk of biliary tract cancer or liver transplantation.

Keywords: primary sclerosing cholangitis; inflammatory bowel disease; biliary tract cancer; thiopurines; anti-TNF.

INTRODUCTION

Crohn's disease and ulcerative colitis, collectively referred to as inflammatory bowel disease (IBD), are lifetime inflammatory gastrointestinal disorders of unknown origin. The diagnosis of Primary Sclerosing Cholangitis (PSC) is made in 1 to 5% of patients with IBD.[1] Conversely, 30-80% of patients with PSC are diagnosed with IBD before, at or after the diagnosis of PSC.[2,3] Patients with an established diagnosis of PSC and IBD (PSC-IBD) are followed jointly by gastroenterologists and liver specialists. For gastroenterologists who manage patients with IBD and PSC, the two main objectives are: to try to obtain a sustained control of intestinal inflammation,[4,5] using increasingly for this purpose thiopurines and tumor necrosis factor antagonists (anti-TNF);[6] to prevent/detect colorectal neoplasia.[7,8] For liver specialists who manage PSC, the main objectives are to limit the progression of hepatobiliary damage, avoid severe biliary sepsis, detect biliary tract malignancies, and indicate when possible and appropriate liver transplantation.[9–11] Exposure to thiopurines and anti-TNF has been associated with an excess risk of various cancers[12] and serious infections[13] in patients with IBD. From a conceptual point of view, one could fear that thiopurines and/or anti-TNF promote PSC-associated malignancies and/or serious biliary infections. While the risks of the main complications of PSC-IBD have been recently quantified in a nationwide cohort,[14] little or no data is available on the impact of exposure to thiopurines and/or anti-TNF on the risk of PSC complications. To our knowledge, only the absence of overt excess of cholangiocarcinoma[15,16] and other PSC main outcomes[16] has been reported in patients with PSC-IBD exposed to thiopurines.

In this study, we identified in the nationwide French administrative health database patients with PSC-IBD and assessed the impact of exposure to thiopurines and/or anti-TNF on two major outcomes of PSC, namely biliary tract cancer and liver transplantation.

METHODS

Data sources

This cohort study was based on the French National health insurance database (*Système National des Données de Santé*, SNDS), which covers 95% of the French population with different insurance schemes based on employment situation.

The SNDS provides individual data on all drug reimbursements, medical procedures and outpatient medical care. Additionally, the SNDS includes information on individuals' status with respect to full reimbursement of care for severe long-term diseases (LTD), including CD, UC, and PSC. Using a unique anonymous identifier, outpatient data are 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.[13,17,18]

This study was approved by the French Data Protection Supervisory Authority (*Commission Nationale de l'Informatique et des Libertés*, authorisation number 918364). All data used in this study contained only anonymous patient records. Patient informed consent was not required because the databases were de-identified.

Study population

The source population included all patients aged 18 years and older identified with PSC and IBD before January 1, 2018 based on data from the SNDS. Identification of IBD cases was based on a previously published algorithms,[13,17] and was defined as the obtaining of LTD's status for CD or UC and/or the existence of at least one hospitalisation discharge with a primary or related diagnosis code related to CD or UC. In case of multiple hospitalisations with ICD-10 codes related to UC or CD, the most recent diagnosis at cohort entry was retained. The date of IBD diagnosis was defined as the earliest date between the starting date of the LTD status and the first date of hospitalisation discharge with a primary or related diagnosis related to CD or UC. Patients with a single hospital discharge diagnosis of IBD and no pharmacy claim for any IBD medication (enteral budesonide, aminosalicylates, thiopurines, anti-TNF, vedolizumab, ustekinumab, and tofacitinib) were considered to have an unconfirmed diagnosis of IBD.

Since the ICD-10 code related to PSC (K83.0, cholangitis) is not specific to PSC, and can be attributed to cholangitis unrelated to PSC, we developed a diagnostic algorithm of PSC identification based on four parameters which are potential direct or indirect diagnostic markers of PSC: hospital discharge diagnosis code related to cholangitis (as primary, related, or associated diagnoses); LTD status validation related to PSC; first dispensation of ursodeoxycholic acid (UDCA), a drug that is prescribed on a long-term basis in most patients with PSC in France; occurrence of a liver biopsy. The diagnosis of PSC was retained in presence of at least two of these four parameters; the date of confirmed PSC identification was the date associated with the second parameter of the algorithm in chronological order.

In order to assess the accuracy of our identification algorithm used for selecting patients with PSC, we performed a validation analysis in the high-granularity research/care SUVIMIC Saint-Antoine health database.[19] Among patients regularly followed in our institution from January 2017 to May 2021, we selected all patients with any clinical, radiological or therapeutic (exposure to ursodeoxycholic acid) feature of PSC, using pre-defined database items and free text research. We identified patients with no PSC, confirmed PSC, or possible PSC. Among the latter patients, we reviewed exhaustively the medical files in order to arbitrate between confirmed cases of PSC and suspected, but not confirmed, cases of PSC. We assessed the positive predictive value (PPV) (whether patients identified with the developed algorithm had a medically confirmed diagnosis of PSC) and sensitivity (whether patients with a medically confirmed diagnosis of PDC were identified with the developed algorithm), using the French national hospital discharge restricted to Saint-Antoine hospital.

Among patients identified with PSC and IBD in our study, we first excluded patients with hospitalisation codes or LTD status related to primary biliary cholangitis or cystic fibrosis since UDCA can be administered for these two diseases (Supplementary Table 1). Second, in order to assess only incident events, we excluded patients with history of liver transplantation, biliary tract cancer, or any other cancer except non-melanoma skin cancers (NMSC) prior to entry into the cohort. Third, to improve the specificity of the PSC-IBD cohort, we excluded patients with an unconfirmed diagnosis of IBD.

Follow-up

Patients diagnosed with PSC and IBD before January 1, 2009 were referred to as having prevalent cases of PSC-IBD (Supplementary Figure 1). Patients diagnosed with PSC and IBD between January 1, 2009 and December 31, 2017 accounted for incident cases of PSC-IBD. Patients with incident PSC-IBD were followed-up from the date of the most recent diagnosis between that of PSC and that of IBD. Since immunosuppressants other than thiopurines and anti-TNF may have an impact of the risk of cancer, we censored patients follow-up when a treatment with ustekinumab, vedolizumab, or tofacitinib was initiated. Considering that therapeutic management of PSC-IBD may be different after occurrence of cancer and that liver transplantation may be contra-indicated in this setting, patient follow-up was censored on the date of diagnosis of any cancer, except non-melanoma skin cancers. Thus, patients were followed up until December 31, 2018; occurrence of liver transplantation; occurrence of any cancer except non-melanoma skin cancer; loss to follow-up or death, whichever occurred first. In case of loss to follow-up (defined as no more contact until December 31, 2018), end of follow-up was the last known contact date, defined by the last claim in the database. In order to minimize the inclusion of prevalent cases of biliary tract cancer or liver transplantation, we considered for each patient a 6-month exclusion period from the date of entry into the observation period (January 1, 2009 for prevalent case, and the date of the most recent diagnosis between that of PSC and that of IBD for incident cases), i.e., we did not take into account cases of biliary tract cancer or liver transplantation that occurred within the 6-month interval after entry into the observation period.

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, golimumab, or thiopurines were considered exposed for one month following each delivery. Combination therapy was defined as the concomitant exposure of anti-TNF 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. We considered that a time interval of up to 6 months may be necessary to confirm the diagnosis of a suspected cancer, or to perform liver transplantation when indicated. Thus, to minimize the risk of falsely attributing an event of interest to a recent change of drug exposure status, exposure time during follow-up started 6 months after treatment initiation and was extended 6 months after treatment switch or withdrawal. The Anatomical Therapeutic Chemical (ATC) codes used to define drug exposures are detailed in Supplementary Table 2.

Outcomes

Study primary outcome was the first incident event among biliary tract cancer and liver transplantation. Biliary tract cancer was defined as the obtaining of LTD's status for biliary tract cancer and/or the existence of at least one hospitalisation with primary ICD-10 discharge code related to biliary tract cancer. Biliary tract cancers included intra and extra-hepatic, perihilar forms of cholangiocarcinoma, and gallbladder carcinoma. The date of

diagnosis was defined as the earliest diagnosis date between the starting date of the LTD status and discharge date of the first cancer-related hospitalisation. Liver transplantation was defined by procedure codes related to liver transplantation. Some patients may undergo liver transplantation without preoperative suspicion of biliary tract cancer, and be secondarily diagnosed with biliary cancer after histological assessment of liver explant. The date of the liver transplantation was considered as the date of the two events. The ICD-10 and *Classification Commune des Actes Médicaux* (CCAM) codes used to define outcomes are detailed in Supplementary Table 3.

Covariates

Time-fixed covariates were measured at cohort entry and included demographic characteristics (age and sex), IBD subtype and comorbidities, IBD duration prior to entry as continuous variable, previous exposure to anti-TNF, thiopurines, methotrexate, and 5-aminosalicylates within six months prior to cohort entry, history of IBD-related surgery and hospitalisation, digestive imaging (Ultrasound, magnetic resonance imaging, and CT-scan) and endoscopy of the digestive tract within six months prior to cohort entry. Comorbidities included history of cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, chronic kidney disease, diabetes, cirrhosis and cirrhosis complications (GI bleeding related to portal hypertension, ascites, encephalopathy, and portal vein thrombosis), obesity, alcohol use disorder, and smoking behavior. Time-varying covariates were related to PSC clinical activity and management, and were updated every three months. These covariates included PSC-related hospitalisations, endoscopic/radiological biliary drainages, and chronic liver diseases (including cirrhosis

complicated or not, viral, metabolic, autoimmune, toxic hepatitis). The ICD-10, ATC and CCAM codes used to define covariates are detailed in Supplementary Table 4.

Statistical Analyses

Patient characteristics at cohort entry were assessed according to treatment exposure and cumulative incidences of biliary tract cancer and liver transplantation were estimated. Cumulative incidences were also assessed for colorectal cancer and any cancer occurrence except NMSC.

We used marginal structural Cox proportional hazard models adjusted for the time-fixed and time-varying covariates listed to assess the risks of biliary tract cancer and liver transplantation between associated with exposure to thiopurines and anti-TNF. Marginal structural models are appropriate in the presence of time-dependent covariates (markers of PSC activity including PSC-related hospitalisation, chronic liver diseases or biliary drainage) that might be associated with both exposure and outcomes (time-dependent confounders) and could also be affected by past exposure to thiopurines and anti-TNF. Weight calculations were performed as suggested by Cole and Hernán.[20] Detailed statistical method is provided in the supplementary appendix.

Several sensitivity analyses were performed to assess the robustness of the findings: exclusion of patients exposed to thiopurines or anti-TNF prior to entry into the observation period, in order to assess a potential prevalent user bias;[21] exclusion of patients not exposed to UDCA and patients without ICD-10 codes related to PSC, in order to test a more stringent approach of diagnosis of PSC-IBD; exclusion of patients with history of chronic liver diseases at entry (HBV and HCV chronic infection, autoimmune hepatitis,

chronic alcoholic liver disease, hemochromatosis) which can lead to liver transplantation or biliary tract cancer; exclusion of patients with a concomitant diagnosis of autoimmune hepatitis which are potentially treated with thiopurines for autoimmune hepatitis and not IBD; inclusion of patients with a history of cancer prior to entry; no censoring of follow-up at occurrence of non-biliary incident cancers or initiation of a treatment with ustekinumab, vedolizumab, or tofacitinib; setting the length of the exclusion period after entry into the observation period to three months or one year instead of 180 days.

In the SNDS database, causes of death based on death certificate were not comprehensively collected during the study period, so it is impossible to accurately assess liver-related death. To assess the impact of this outcome, we performed a sensitivity analysis by adding the occurrence of death within 3 months after a hospitalization for chronic liver disease to the primary outcome definition.

Analyses were performed using SAS (v9.4) statistical software (SAS Institute).

Results

Characteristics of the study population

Among 305,911 patients diagnosed with IBD up to December 31, 2017, 3031 patients were identified as having PSC, using our identification algorithm. Most patients diagnosed with PSC were identified through exposure to UDCA and hospitalisation with ICD-10 codes related to PSC (Supplementary Table 5).

Among 3807 patients followed in the Saint-Antoine IBD centre between January 2017 and May 2021, we identified using the SUVIMIC database and exhaustive review of medical files of possible cases of PSC, 3667 patients with IBD and no feature of PSC, 117 patients

with IBD and confirmed PSC, and 23 patients with IBD and suspected, but not confirmed, PSC. Considering the diagnosis of confirmed PSC as a gold standard, the positive predictive value of the identification algorithm was 100% while the sensitivity was 89.7%. Among the 3031 patients identified in the SNDS with PSC-IBD, 228 were younger than 18 years at diagnosis, 256 had a history of primary biliary cholangitis or cystic fibrosis,154 had liver transplantation prior to cohort entry, 327 had a history of cancer other than non-melanoma kin cancer (including 62 cases of biliary tract cancer) prior to cohort entry, and 137 had an unconfirmed diagnosis of IBD (Figure 1). Thus, a total of 1929 patients with PSC-IBD ultimately constituted the study population subjected to follow-up.

Patient characteristics at entry into the observation period according to treatment exposure during follow-up are summarised in Table 1. The mean IBD and PSC disease durations at entry into the observation period were 6.9 years (standard Deviation [SD], 6.8) and 2.2 years (SD, 2.6), respectively. Most patients were males (56.2%) and the mean age of patients at entry was 41.5 years (SD, 15.5). The majority of patients were diagnosed with UC (n=1025, 53.1%), notably among patients unexposed to thiopurines or anti-TNF (n=555, 60.5%). 25.3% and 43.9% of patients had previously been treated with anti-TNF and thiopurines prior to entry into the observation period. 14.4% of patients with PSC-IBD had a cirrhosis at baseline. 114 (5.9%) patients had associated autoimmune hepatitis at entry (Table 1) and 160 (8.3%) patients had a diagnosis of autoimmune hepatitis at any time during the study period.

During follow-up, 673 (34.9%) and 625 (32.4%) patients were exposed to thiopurines or anti-TNF, respectively. Among patients exposed to thiopurines, 68.8% (n=463) had previously been exposed to thiopurines prior to entry into the observation period. Among patients exposed to anti-TNF, 354 (56.6%) had previously been exposed to anti-TNF. A

total of 237 (12.3%) patients were exposed to the combination of anti-TNF and thiopurines during the follow-up.

Incidence of biliary tract cancer tract and liver transplantation

Overall, the 1929 patients of the study population were followed for a total period of 9827 person-years (PY). Mean follow-up time was 5.1 (SD, 3.2) years in the total population, 4.7 (SD, 3.3), 5.7 (SD, 2.9), and 5.2 (SD, 3.0), in patients not exposed to thiopurines or anti-TNFs, exposed to thiopurines, and exposed to anti-TNFs during follow-up, respectively. Biliary tract cancer and liver transplantation, as primary outcomes, occurred as the first censoring event in 37 (1.9%) and 83 (4.3%) patients, respectively. In one patient, biliary tract cancer and liver transplantation occurred simultaneously. Thus, 120 events occurred in 119 patients, resulting in an overall incidence rate of 12.1 per 1000 PY. Incidence rates were of 3.8 per 1000 PY and 8.4 per 1000 PY for biliary tract cancers and liver transplantation, respectively. The 10-year cumulative risks of biliary tract and liver transplantation were 4.0% (95% CI, 2.8-5.5) and 8.3% (95% CI, 6.6-10.3), respectively (Figure 2). The overall 10-year risk of biliary tract cancer and/or liver transplantation was 11.8% (95% CI, 9.7-14.1). Incidence rates of biliary tract cancer and/or liver transplantation by drug exposure are provided in Table 2, and cumulative incidences of liver transplantation or biliary tract cancer by exposure group are provided in Supplementary Figure 2. Patient characteristics according to outcome occurrence during follow-up are provided in Table 3.

Incidence of colorectal cancer or any cancer, except NMSC

Among the 1929 patients of the study population, 35 (1.8%) developed colorectal cancer as first incident cancer, resulting in an incidence rate of 3.6 per 1000 PY. The 10-year cumulative risk of colorectal cancer was 3.1% (95% CI, 2.1-4.4). Sixty-one (3.2%) patients developed any cancer except NMSC as first censoring event, resulting in an overall incidence rate of 8.2 per 1000 PY. The 10-year cumulative risk of developing any cancer except NMSC was 5.9 % (95% CI, 4.4-7.7).

Risk of biliary tract cancer and liver transplantation according to drug exposure

Compared with patients unexposed to thiopurines and anti-TNF, patients exposed to thiopurines were not at excess risk of biliary tract cancer (hazard ratio [HR], 1.05; 95% confidence interval [CI], 0.39-2.82) and liver transplantation (HR, 0.67; 95% CI, 0.30-1.48). Compared with patients unexposed to thiopurines and anti-TNF, patients exposed to anti-TNF were not at excess risk of biliary tract cancer (HR: 0.59 95% CI, 0.13-2.80) and liver transplantation (HR: 0.68, 95% CI, 0.22-2.09). Results were similar (Figure 3) regarding; the combined risk of biliary tract cancer and/or liver transplantation, both in patients exposed to thiopurines and to anti-TNF; the risk of biliary tract cancer and/or liver transplantation in patients exposed to combination therapy of thiopurines and anti-TNF. HRs were not substantially changed (Table 4) in the different sensitivity analyses. Adding the occurrence of death within 3 months after a hospitalization for chronic liver disease to the primary outcome definition, did not impact the main findings (HR: 0.68 95% CI, 0.36-1.31, HR: 0.59, 95% CI, 0.24-1.45, HR: 0.41 95% CI, 0.12-1.35, in patients exposed to thiopurines, anti-TNFs, and combination therapy, respectively)

DISCUSSION

Based on a large population-based nationwide cohort of patients with PSC-IBD, our findings suggest that the exposure to thiopurines and/or anti-TNF has no deleterious impact on the risk of biliary tract cancer and liver transplantation.

Patients with IBD exposed to thiopurines exhibit an excess risk of various hematological malignancies, urinary tract cancers and non-melanoma skin cancers.[12] Patients with PSC are at high risk of cholangiocarcinoma and gallbladder cancer compared with age and gender-matched controls from the general population.[14] In a retrospective study by Zenouzi et al. from three tertiary care centers, there was no evidence that exposure to azathioprine further increases the risk of cholangiocarcinoma in patients with PSC.[15] We confirm this result in our study that differs in some points from the previous one: our study was population-based, featured a total number of person-years almost doubled, and results were adjusted for time-fixed and time-varying covariates.

Patients with IBD exposed to anti-TNF are at mild excess risk of melanomas.[22] Whether ant-TNFs promote other types of cancers is still a matter of debate, especially with regard to lymphomas.[17,23] To our knowledge, the impact of anti-TNF on the risk of biliary tract cancer has not been specifically studied to date. Our study provides a first reassuring signal in this field.

Patients with an association of autoimmune hepatitis and PSC should be considered separately in terms of natural history and propensity to receive thiopurines. Major trends of the study were not affected in a sensitivity analysis that excluded patients with a concomitant diagnosis of autoimmune hepatitis.

In patients with IBD, chronic inflammation of the digestive tract is considered as an independent driver of the risk of colorectal cancer, small bowel adenocarcinoma and anal cancers.[7,24] Thiopurines and anti-TNF can reduce the inflammation in intestinal segments that are affected by IBD, which can in turn reduce the risk of inflammation-related cancers. This chemopreventive effect of immune-suppressive drugs in the risk of colorectal has been suggested in patients with UC for thiopurines in two nationwide cohorts.[25,26] In our study, we did not observe a reduced risk of biliary tract cancer in patients with PSC-IBD exposed to thiopurines and/or anti-TNF. This absence of chemopreventive effect of thiopurines and anti-TNF is consistent with the lack of definite proof of efficacy of thiopurines and anti-TNF on chronic inflammatory lesions of PSC,[27,28] despite the fact that a decreased risk of death or liver transplantation has been suggested in a recent Swedish population-based cohort.[16]

Exposure to thiopurines and anti-TNF had no obvious impact on the time of liver transplantation in patients with PSC-IBD. Thiopurines and anti-TNF promote all types of serious infections.[13] From a conceptual point of view, we could therefore have hypothesised that thiopurines and anti-TNF promote repeated infections of the bile ducts, this leading to a more rapid progression of biliary and liver lesions, and therefore to an earlier indication of liver transplantation. Conversely, the need for liver transplantation could have been reduced if thiopurines and anti-TNF had had an established slowing effect on the progression of biliary and liver lesions in PSC. But, as mentioned above, this impact has not been fully demonstrated to date.[16,27,28]

Our study has several strengths. 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 PSC-IBD 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. This design increases the generalizability of the findings reported, while the majority of studies assessing the clinical course of PSC are based on tertiary care centers. It is the first observational study that evaluates the risk of exposure to main immunosuppressive IBD-drugs, notably anti-TNF, on poor PSC outcomes. Analyses were adjusted for a variety of confounding factors including co-treatment exposure, comorbidities, IBD and PSC disease severity. Lastly, these findings were consistent across several sensitivity analyses.

The main potential limitation of our study was the use a specifically-designed classification algorithm for identifying patients with PSC, given the fact that the ICD code available in the SNDS does not distinguish between PSC and other causes of cholangitis. However, we were able to validate our algorithm in a phenotyped-in-depth tertiary care IBD population. All patients identified with PSC using the algorithm had a medically confirmed diagnosis of PSC, and the vast majority of patients with IBD and PSC were correctly selected. This may explain why the proportion of patients with IBD who were identified with PSC in our cohort was similar or slightly lower than that reported in nationwide studies,[14,29] or in a recent meta-analysis.[30] Nevertheless, future studies will benefit from the recently introduced ICD-11 code for PSC (K83.01) to overcome these limitations.

We acknowledge, however, some other limitations. First, baseline adjustment for IBD activity and time-dependent adjustment for PCS activity were not based on continuous recording of disease activity, but to indirect markers of activity, including hospitalisations/diagnostic procedures for disease flares and disease complications. Second, we were not able to adjust our multivariate analysis for the suspected inverse relation between clinical and anatomical severity of intestinal and biliary disease.[31]

However, we included the IBD subtype and baseline IBD disease activity in the analysis, in order to adjust for the fact that the need for liver transplantation has been suggested to be lower in Crohn's disease than in ulcerative colitis,[32] while patients with Crohn's disease are more exposed to immunosuppressants. Finally, we must emphasize the limited power of our study, resulting in wide confidence intervals of the HR. We had 80% power to rule out a theoretical 1.7-fold increase of biliary tract cancer or liver transplantation in patients either exposed to thiopurines or anti-TNFs, while a total number of 32 000 PY would have been necessary to rule out with a beta risk of 20% a 1.2-fold increase of the risk of biliary tract cancer or liver transplantation in patients either exposed to thiopurines or anti-TNFs. Therefore, caution should be made in the interpretation of results, especially in patients exposed to combination of thiopurines and anti-TNF, given the limited subgroup size.

The incidence of liver transplantation, although lower than that observed in studies restricted to tertiary care centers,[3] was of the same extent as that reported in a recent nationwide English cohort.[14] By contrast, in our study, the incidence of biliary tract was substantially lower than in the English cohort. This discrepancy can be attributed to the fact that up to one third of biliary tract cancers are diagnosed within the first year following the diagnosis of PSC, while in our cohort: mean duration of PSC at entry into the observation period was two years; biliary tract cancers that occurred before entry were excluded; cancers that occurred within the 6 first months of the observation period were not taken into account.

In summary, our study suggests that the exposure to thiopurines and/or anti-TNF has no deleterious impact on the risk of biliary tract cancer and liver transplantation in patients with PSC-IBD. Although these results must be replicated in an independent cohort, we provide a first reassuring signal for physicians who were hesitating to treat on a long-term

basis IBD with thiopurines and/or anti-TNF patients with PSC-IBD, for fear of increasing the risk of biliary cancer and severe hepatobiliary damage.

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Table 1. Patient characteristics at entry into the observation period according to drug exposure during follow-up.

	Unexposed to thiopurines and anti-TNF during follow-up (n = 918)	Exposed to thiopurines[a] during follow-up (n = 673)	Exposed to Anti-TNF[a] during follow-up (n = 625)	All[a] (n = 1929)
Male sex, n (%)	537 (58.5)	374 (55.6)	329 (52.6)	1085 (56.2)
Age, mean (SD)	44.7 (15.9)	36.8 (14.2)	38.6 (14.0)	41.5 (15.5)
Complementary universal health insurance, n(%)[b]	77 (8.4)	77 (11.4)	80 (12.8)	201 (10.4)
IBD duration, *y*, mean (SD)	7.4 (6.9)	5.6 (6.4)	6.9 (6.5)	6.9 (6.8)
Mean PSC duration, *y*, mean (SD)	2.5 (2.9)	1.9 (2.3)	1.8 (2.3)	2.2 (2.6)
IBD subtype				
Crohn disease, n (%)	363 (39.5)	339 (50.4)	356 (57.0)	904 (46.9)
Ulcerative colitis, n (%)	555 (60.5)	334 (49.6)	269 (43.0)	1025 (53.1)
IBD treatment[c], n (%)				
Anti-TNF	113 (12.3)	150 (22.3)	354 (56.6)	489 (25.3)
Thiopurines	199 (21.7)	463 (68.8)	384 (61.4)	846 (43.9)
Methotrexate	61 (6.6)	17 (2.5)	70 (11.2)	142 (7.4)
Aminosalicylates	764 (83.2)	447 (66.4)	437 (69.9)	1458 (75.6)
Hospitalisations[c], n (%)				
IBD-related hospitalisation	144 (15.7)	159 (23.6)	190 (30.4)	401 (20.8)
IBD-related surgery	89 (9.7)	79 (11.7)	109 (17.4)	230 (11.9)
Hospitalisation not related to IBD, n (%)	315 (34.3)	234 (34.8)	206 (33.0)	667 (34.6)
IBD disease activity assessment[c], n (%)				
Endoscopy of the digestive tract	547 (59.6)	402 (59.7)	382 (61.1)	1155 (59.9)
Imaging exams of the digestive tract[d]	568 (61.9)	428 (63.6)	397 (63.5)	1206 (62.5)
Complications related to PSC[e], n (%)				
Hospitalisations related to PSC	225 (24.5)	145 (21.5)	105 (16.8)	422 (21.9)
Cirrhosis	127 (13.8)	97 (14.4)	89 (14.2)	277 (14.4)
Complications of cirrhosis[f]	61 (6.6)	36 (5.3)	38 (6.1)	122 (6.3)
Comorbidities, n (%)				
Chronic Liver disease	177 (19.3)	184 (27.3)	131 (21.0)	431 (22.3)
Autoimmune hepatitis	32 (3.5)	73 (10.8)	27 (4.3)	114 (5.9)
Cardiovascular disease	113 (12.3)	56 (8.3)	66 (10.6)	217 (11.2)
Cerebrovascular disease	19 (2.1)	6 (0.9)	11 (1.8)	36 (1.9)
Peripheral vascular disease	17 (1.9)	15 (2.2)	12 (1.9)	40 (2.1)
Chronic pulmonary disease	200 (21.8)	125 (18.6)	129 (20.6)	411 (21.3)
Chronic kidney disease	17 (1.9)	11 (1.6)	9 (1.4)	33 (1.7)
Inflammatory Rheumatism	49 (5.3)	38 (5.6)	88 (14.1)	156 (8.1)
Venous thromboembolism disease	36 (3.9)	25 (3.7)	28 (4.5)	77 (4.0)
Hypertension	246 (26.8)	136 (20.2)	139 (22.2)	476 (24.7)
Diabetes	90 (9.8)	64 (9.5)	54 (8.6)	190 (9.8)
Dyslipidemia	195 (21.2)	131 (19.5)	126 (20.2)	396 (20.5)
Alcohol use disorder	39 (4.2)	22 (3.3)	28 (4.5)	78 (4.0)
Smoking behavior	43 (4.7)	44 (6.5)	63 (10.1)	129 (6.7)
Obesity	70 (7.6)	52 (7.7)	56 (9.0)	158 (8.2)

Abbreviations: SD, standard deviation; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

[a] Patients exposed to combination of anti-TNF and thiopurines at any time during the follow-up were included both in the group of patients exposed to anti-TNF and in the group of patients exposed to thiopurines.

[b] Free access to health care for all French people whose annual income is less than half the poverty line.

[c] Within 6 months prior to entry into the observation period.

[d] Ultrasound, magnetic resonance imaging, CT-scan.

[e] At any time between PSC diagnosis and entry into the observation period.

[f] GI bleeding related to portal hypertension, ascites, encephalopathy, and portal vein thrombosis

Table 2. Incidence rates of biliary tract cancer and/or liver transplantation according to drug exposure.

	All (9,827 PY)		Unexposed to thiopurines and anti-TNF during follow-up (6,223 PY)		Exposed to thiopurines[a] during follow-up (2,022 PY)		Exposed to Anti-TNF[a] during follow-up (2,015 PY)	
	Events	IR[b] (95% CI)	Events	IR[b] (95% CI)	Events	IR[b] (95% CI)	Events	IR[b] (95% CI)
Biliary tract cancer and/or liver transplantation	119	12.1 (10.1-14.5)	89	14.3 (11.6-17.6)	21	10.4 (6.8-15.9)	10	5.0 (2.7-9.2)
Biliary tract cancer	37	3.8 (2.7-5.2)	30	4.8 (3.4-6.9)	4	2.0 (0.7-5.3)	3	1.5 (0.5-4.6)
Liver transplantation	83	8.4 (6.8-10.5)	60	9.6 (7.5-12.4)	17	8.4 (5.2-13.5)	7	3.5 (1.6-7.3)

Values are n (incidence rate/1000 person-years). Abbreviations: PY, person-years.
[a] patients exposed to combination of anti-TNF and thiopurines at any time during the follow-up were included both in the group of patients exposed to anti-TNF and in the group of patients exposed to thiopurines.
[b] Incidence rates per 1000 person-years
Abbreviations: PY, person-years; TNF, Tumor Necrosis Factor

Table 3. Patient characteristics at entry into the observation period according to outcome occurrence during follow-up.

	Absence of biliary tract cancer tract and liver transplantation (n = 1810)	Biliary tract cancer tract or liver transplantation occurrence (n = 119)	All (n = 1929)
Male sex, n (%)	1007 (55.6)	78 (65.5)	1085 (56.2)
Age, mean (SD)	41.8 (15.6)	37.6 (13.2)	41.5 (15.5)
Complementary universal health insurance, n(%)[a]	182 (10.1)	19 (16.0)	201 (10.4)
IBD duration, *y*, mean (SD)	6.9 (6.8)	7.0 (6.9)	6.9 (6.8)
Mean PSC duration, *y*, mean (SD)	2.1 (2.6)	2.9 (2.3)	2.2 (2.6)
IBD subtype			
Crohn disease, n (%)	860 (47.5)	44 (37.0)	904 (46.9)
Ulcerative colitis, n (%)	950 (52.5)	75 (63.0)	1025 (53.1)
IBD treatment[b], n (%)			
Anti-TNF	481 (26.6)	8 (6.7)	489 (25.3)
Thiopurines	797 (44.0)	49 (41.2)	846 (43.9)
Methotrexate	141 (7.8)	1 (0.8)	142 (7.4)
Aminosalicylates	1377 (76.1)	81 (68.1)	1458 (75.6)
Hospitalisations[b], n (%)			
IBD-related hospitalisation	374 (20.7)	27 (22.7)	401 (20.8)
IBD-related surgery	221 (12.2)	9 (7.6)	230 (11.9)
Hospitalisation not related to IBD, n (%)	616 (34.0)	51 (42.9)	667 (34.6)
IBD disease activity assessment[b], n (%)			
Endoscopy of the digestive tract	1077 (59.5)	78 (65.5)	1155 (59.9)
Imaging exams of the digestive tract[c]	1136 (62.8)	70 (58.8)	1206 (62.5)
Complications related to PSC[d], n (%)			
Hospitalisations related to PSC	374 (20.7)	48 (40.3)	422 (21.9)
Cirrhosis	249 (13.8)	28 (23.5)	277 (14.4)
Complications of cirrhosis[e]	115 (6.4)	7 (5.9)	122 (6.3)
Comorbidities, n (%)			
Chronic liver disease	404 (22.3)	27 (22.7)	431 (22.3)
Autoimmune hepatitis	105 (5.8)	9 (7.6)	114 (5.9)
Cardiovascular disease	204 (11.3)	13 (10.9)	217 (11.2)
Cerebrovascular disease	34 (1.9)	2 (1.7)	36 (1.9)
Peripheral vascular disease	38 (2.1)	2 (1.7)	40 (2.1)
Chronic pulmonary disease	398 (22.0)	13 (10.9)	411 (21.3)
Chronic kidney disease	32 (1.8)	1 (0.8)	33 (1.7)
Inflammatory Rheumatism	151 (8.3)	5 (4.2)	156 (8.1)
Venous thromboembolism disease	70 (3.9)	7 (5.9)	77 (4.0)
Hypertension	458 (25.3)	18 (15.1)	476 (24.7)
Diabetes	185 (10.2)	5 (4.2)	190 (9.8)
Dyslipidemia	374 (20.7)	22 (18.5)	396 (20.5)
Alcohol use disorder	72 (4.0)	6 (5.0)	78 (4.0)
Smoking behavior	129 (7.1)	0 (0)	129 (6.7)
Obesity	148 (8.2)	10 (8.4)	158 (8.2)

Abbreviations: SD, standard deviation; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.
[a] Free access to health care for all French people whose annual income is less than half the poverty line.
[b] Within 6 months prior to entry into the observation period.
[c] Ultrasound, magnetic resonance imaging, CT-scan.
[d] At any time between PSC diagnosis and entry into the observation period.
[e] GI bleeding related to portal hypertension, ascites, encephalopathy, and portal vein thrombosis

Table 4. Sensitivity analyses: multivariable adjusted Hazard ratios (HR) for biliary tract cancer and/or liver transplantation according to treatment exposure between patients exposed to thiopurines and/or anti-TNF and patients unexposed to thiopurines and anti-TNF.

	Risk of biliary tract cancer HR (95% CI)	Risk of liver transplantation HR (95% CI)	Risk of biliary tract cancer liver and/or liver transplantation HR (95% CI)
Exclusion of patients exposed to thiopurines or anti-TNF prior to entry			
Thiopurines	[a]	0.96 (0.18-5.25)	0.43 (0.09-2.00)
Anti-TNF	1.10 (0.16-7.77)	1.55 (0.47-5.09)	1.27 (0.44-3.64)
Combination therapy	[a]	1.49 (0.17-12.8)	0.54 (0.08-3.75)
Exclusion of patients not previously exposed to UDCA			
Thiopurines	1.07 (0.39-2.90)	0.68 (0.30-1.54)	0.79 (0.40-1.52)
Anti-TNF	0.59 (0.13-2.73)	0.65 (0.22-1.98)	0.61 (0.26-1.47)
Combination therapy	0.63 (0.09-4.50)	0.44 (0.10-1.95)	0.48 (0.15-1.58)
Exclusion of patients without any ICD-10 codes related to PSC			
Thiopurines	1.30 (0.47-3.58)	0.68 (0.27-1.71)	0.84 (0.41-1.74)
Anti-TNF	0.33 (0.05-2.08)	0.56 (0.16-2.00)	0.48 (0.17-1.31)
Combination therapy	0.43 (0.05-3.94)	0.38 (0.07-2.08)	0.40 (0.11-1.52)
Exclusion of patients with history of chronic liver disease			
Thiopurines	0.97 (0.25-3.78)	0.46 (0.12-1.70)	0.67 (0.24-1.86)
Anti-TNF	0.86 (0.14-5.16)	0.45 (0.12-1.70)	0.76 (0.25-2.28)
Combination therapy	0.83 (0.08-9.03)	0.21 (0.02-1.77)	0.51 (0.10-2.69)
Exclusion of patients with concomitant diagnosis of autoimmune hepatitis			
Thiopurines	1.08 (0.38-3.08)	0.98 (0.37-2.60)	1.01 (0.50-2.05)
Anti-TNF	0.61 (0.13-2.80)	0.47 (0.13-1.71)	0.54 (0.20-1.42)
Combination therapy	0.66 (0.09-4.69)	0.46 (0.08-2.58)	0.55 (0.15-2.00)
No censoring at occurrence of non-biliary incident cancers or treatment switch			
Thiopurines	0.80 (0.28-2.29)	0.75 (0.34-1.64)	0.75 (0.39-1.42)
Anti-TNF	0.39 (0.09-1.69)	0.45 (0.15-1.37)	0.43 (0.18-1.29)
Combination therapy	0.31 (0.04-2.24)	0.34 (0.08-1.37)	0.32 (0.10-1.04)
Remanence period extended to 90 days			
Thiopurines	1.14 (0.42-3.09)	0.47 (0.19-1.13)	0.65 (0.32-1.32)
Anti-TNF	0.74 (0.20-2.70)	0.42 (0.11-1.59)	0.53 (0.22-1.29)
Combination therapy	0.85 (0.15-4.78)	0.20 (0.04-1.04)	0.34 (0.10-1.16)
Remanence period extended to 365 days			
Thiopurines	0.69 (0.202.42)	0.80 (0.38-1.67)	0.74 (0.39-1.42)
Anti-TNF	0.47 (0.11-1.95)	1.11 (0.40-3.08)	0.78 (0.36-1.71)
Combination therapy	0.33 (0.04-2.46)	0.89 (0.22-3.51)	0.58 (0.19-1.76)

Abbreviations: CI, confidence interval; TNF, tumor necrosis factor; UDCA, ursodeoxycholic acid.
[a] No event occurred in the active treatment group

Figure

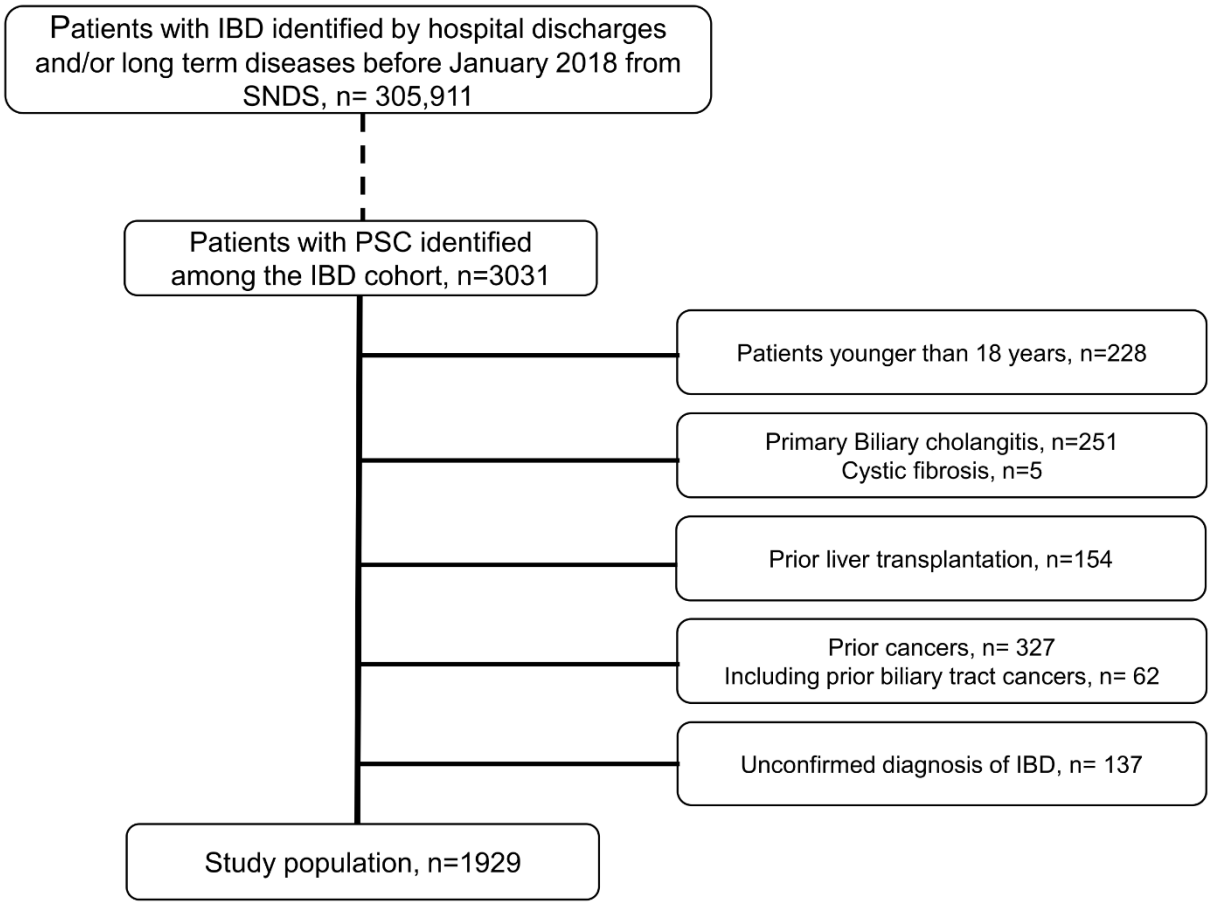

Figure 1. Flow chart of the study population with inflammatory bowel disease (IBD) and primary sclerosing cholangitis (PSC) taken from the French National *Système National des Données de Santé* (SNDS).

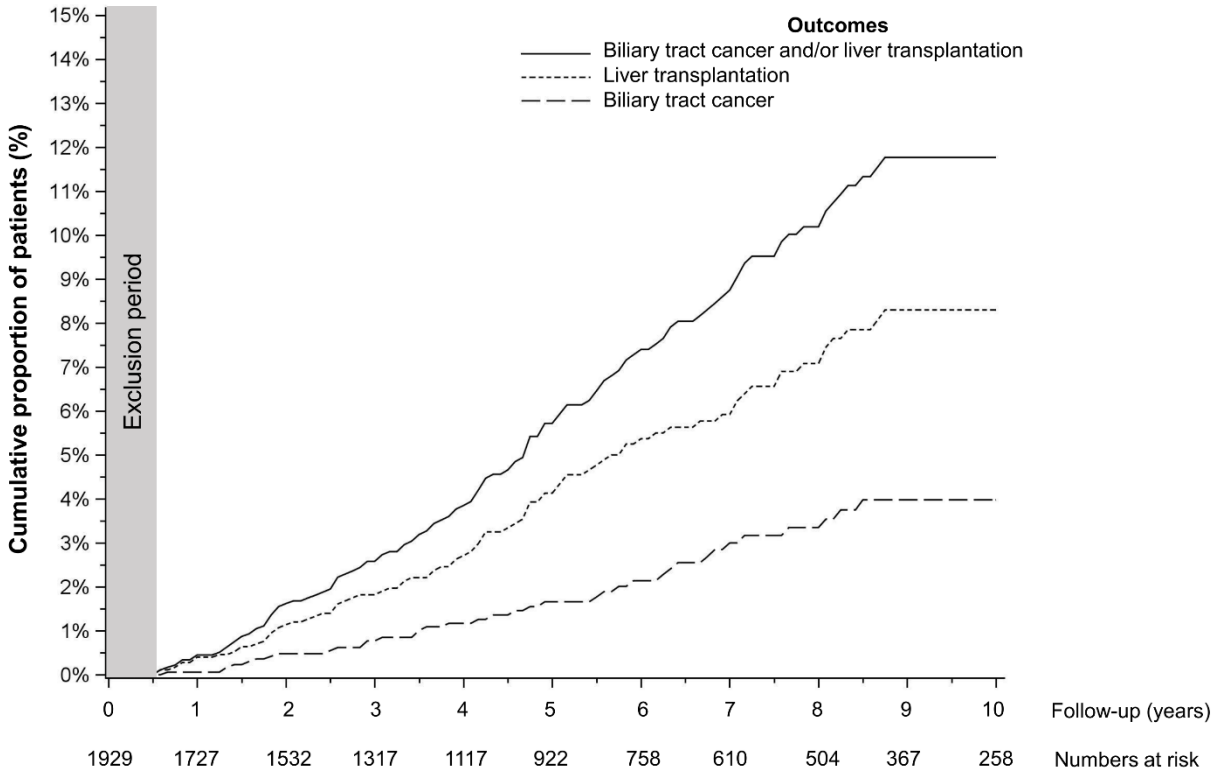

Figure 2. Cumulative incidence of biliary tract cancers and/or liver transplantation as first censoring event during follow up. One patient had simultaneous occurrence of diagnosis of biliary tract cancer and liver transplantation. In all patients, the first 6 months of follow-up refer to the exclusion period in which cases and person-years were not taken into account in the analyses.

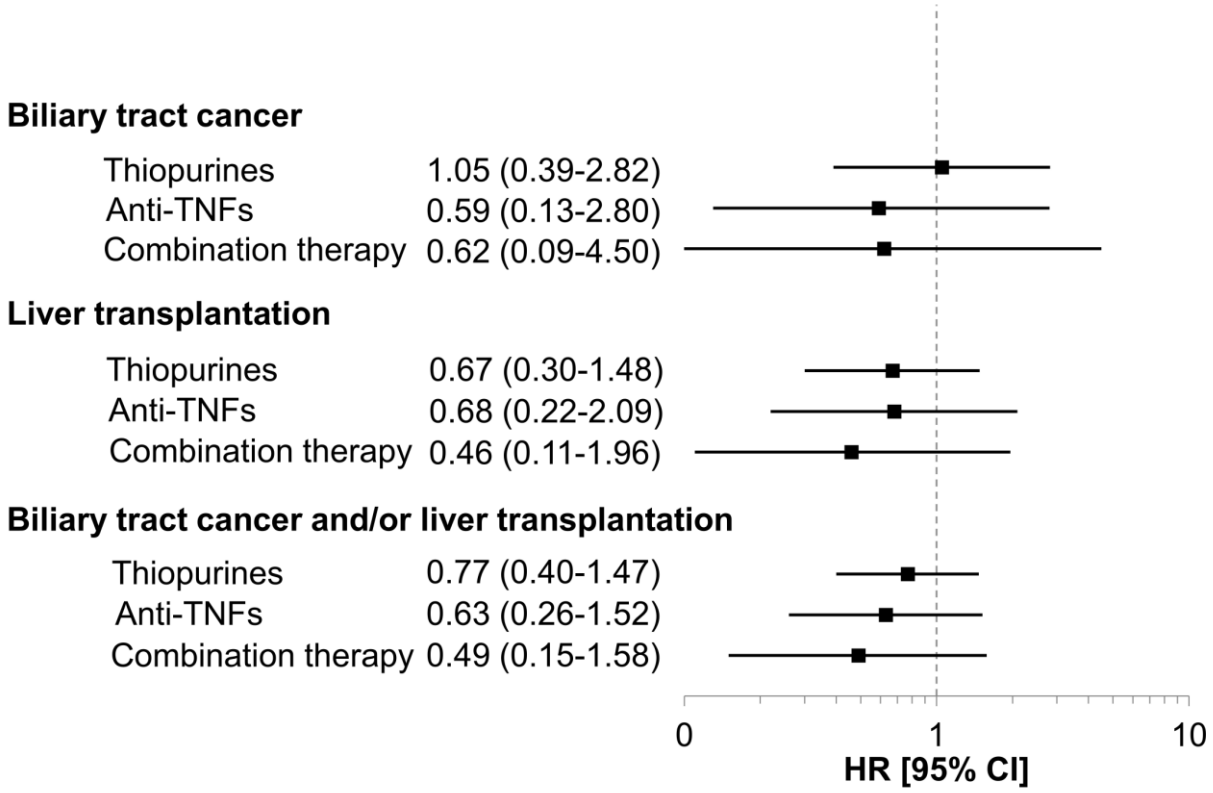

Figure 3. Multivariable adjusted Hazard ratios (HR) for biliary tract cancer and/or liver transplantation according to treatment exposure between patients exposed to thiopurines and/or anti-TNF and patients unexposed to thiopurines and anti-TNF

Supplementary material

Appendix: Methods

The conditional probability of receiving observed treatment was estimated using binomial logistic regression. 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. 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 were truncated at 5th and 95th percentiles to minimize the impact of extreme weights and improve precision.[1,2] The outcome model was adjusted for baseline covariates. An interaction term between anti-TNF and thiopurines exposure was introduced in the outcome model.[3] Robust variance estimators were used to estimate conservative 95% confidence intervals.

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Supplementary Table 1 – Codes used to define exclusion criteria

Comorbidities at cohort entry	**ICD-10 codes** SNDS: primary, related or associated discharge diagnosis
Liver transplant	Z944
Primary biliary cholangitis	K743
Cystic fibrosis	E84
Prior cancers	C1-C9

PSC, Primary sclerosing cholangitis; ICD-10, international classification of diseases, 10th edition; SNDS, Système National des Données de Santé.

Supplementary Table 2 - Codes used to define treatment exposure

Drugs	ATC codes
Adalimumab	L04AB04
Infliximab	L04AB02
Golimumab	L04AB06
Azathioprine	L04AX01
Mercaptopurine	L01BB02
Methotrexate	L04AX03, L01BA01
Sulfazalasine	A07EC01
Mesalazine	A07EC02
Olsalazine	A07EC03
Vedolizumab	L04AA33
Ustekinumab	L04AC05

ATC, Anatomical Therapeutic Chemical.

Supplementary Table 3 – codes used to define outcomes

Outcomes	ICD-10 codes	Procedure codes (CCAM)
Cholangiocarcinoma Gallbladder cancer	C24, C221 C23	
Liver transplantation		HLEA001, HLEA002, HGEA002, HGEA004
Colorectal cancer	C18, C19, C20	
Any cancer	C1-C9	

ICD-10, international classification of diseases, 10th edition; CCAM, Classification Commune des Actes Médicaux.

Supplementary Table 4 – Codes used to define covariates

Comorbidities	ICD-10 codes	Drugs (ATC codes)	Procedures codes (CCAM)
Venous thromboembolism	I26, I80-I82, O22.3, O22.9, O87.1, O88.2	-	
HIV	B20-B24, C46, R75, Z21, F02.4, O98.7	-	
Kidney failure	N18, N19, Z49, Z992, I13.0, I13.1, Y84.1	-	
Respiratory chronic disease	J40-J44, J47, J96.1	-	
Cardiovascular diseases	I74,G45, G46.0-G46.2,I11.0, I13.0, I13.2, I13.9, I20-I25, I50, I60-I66, I67.0-I67.2, I68,I69, I70, K76.1, T82.0,T82.2,T82.3,T82.6,T82.7,Z45.0,Z 86.71, Z95.0-Z95.5		
Rheumatic disease	M05-M09, M45, M35.1, M35.3	-	
Diabetes	E10-E14, M14.2, N08.3, H28.0, H36.0, G59.0, G63.2, I79.2	A10	
Dyslipidemia	E780-E786, E789	C10	
Alcohol use disorder	E244, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, O35.4, T51, X45, X65, Y15, Z50.2, Z71.4	N07BB	
Hypertension	I10-I13, I15	C02, C03, C07, C08, C09	
Smoking behavior	F17, Z71.6, Z72.0, T65.2	N07BA01	
Obesity	E66	-	
Liver disease	K701, K711, K729, K741, K759, K764	-	
Viral hepatitis Autoimmune hepatitis	B171, B16, B170, B18, K754		
Hemochromatosis	E831	-	
Lithiasis	K800, K801, K802, K804, K805, K808	-	
Cholangitis and biliary drainage	K803		HMLE002, HMLE003, HMLH002, HMJH005, HMLH003, HMLH001, HMJH001, HMAH001, HMAH002, HMAE002
Cirrhosis	K700, K703, K717, K721, K740, K741, K742, K744, K745, K746, I859, I982, I864, K766		EHBD001, EHNE001, EHNE002, EHSF001, HPHB003, HPJB001
Complicated cirrhosis	R18, I81, K767, I850, I983, K720, K729		
IBD-related surgery			HHFA008, HHFA010, HHFA023, HHFC296, HHQE003, HHFA002, HHFA004, HHFA005

ICD-10, international classification of diseases, 10th edition; ATC, Anatomical Therapeutic Chemical; CCAM, Classification Commune des Actes Médicaux.

Supplementary Table 5 – Distribution of PSC diagnostic criteria

Parameters	N (%) (n=1929)
ICD-10 codes related to PSC	1395 (72.3)
Hospitalization with ICD-10 codes related to PSC	1330 (69.0)
LTDs with ICD-10 codes related to PSC	204 (10.6)
Exposure to UDCA	1869 (96.9)
Liver biopsy	1176 (61.0)

PSC, primary sclerosing cholangitis; LTD, long-term disease; LTD, long-term disease; UDCA, ursodeoxycholic acid.

Supplementary Figure 1 – Graphical depiction of study follow-up design; (A) IBD and PSC diagnosed before January 1st, 2009; (B) IBD (or PSC) diagnosed before January 1st, 2009 and PSC (or IBD) diagnosed after 2009; (C) IBD and PSC diagnosed after January 1st, 2009

Figure 1A – IBD and PSC diagnosed before January 1st, 2009;

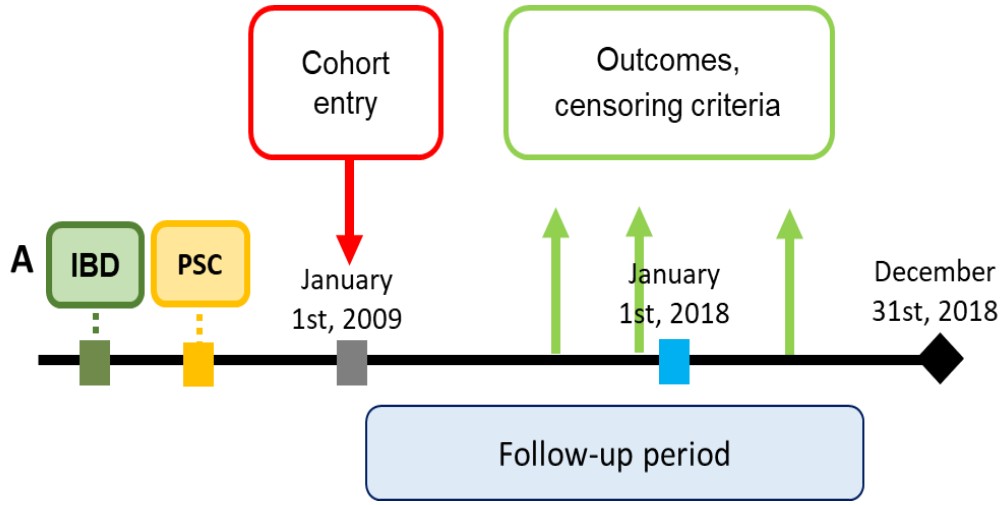

Figure 1B- IBD (or PSC) diagnosed before January 1st, 2009 and PSC (or IBD) diagnosed after 2009 and before January 1st, 2018.

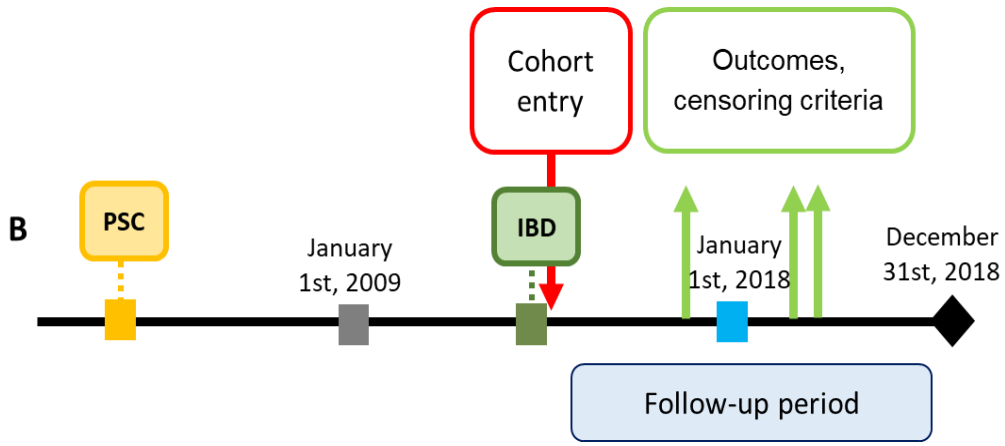

Figure 1C- IBD and PSC diagnosed after January 1st, 2009 and before January 1st, 2018.