Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study

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Summary

Background Reports of an increased risk of lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease are controversial. We assessed this risk in a prospective observational cohort study.

Methods 19 486 patients with inflammatory bowel disease, of whom 11 759 (60·3%) had Crohn's disease and 7727 (39·7%) had ulcerative colitis or unclassified inflammatory bowel disease, were enrolled in a nationwide French cohort by 680 gastroenterologists, who reported details of immunosuppressive therapy during the observation period, cases of cancer, and deaths. The risk of lymphoproliferative disorder was assessed according to thiopurine exposure. Median follow-up was 35 months (IQR 29–40).

Findings At baseline, 5867 (30·1%) of patients were receiving, 2809 (14·4%) had discontinued, and 10 810 (55·5%) had never received thiopurines. 23 new cases of lymphoproliferative disorder were diagnosed, consisting of one case of Hodgkin's lymphoma and 22 cases of non-Hodgkin lymphoproliferative disorder. The incidence rates of lymphoproliferative disorder were 0·90 per 1000 (95% CI 0·50–1·49) patient-years in those receiving, 0·20/1000 (0·02–0·72) patient-years in those who had discontinued, and 0·26/1000 (0·10–0·57) patient-years in those who had never received thiopurines (p=0·0054). The multivariate-adjusted hazard ratio of lymphoproliferative disorder between patients receiving thiopurines and those who had never received the drugs was 5·28 (2·01–13·9, p=0·0007). Most cases associated with thiopurine exposure matched the pathological range of post-transplant disease.

Interpretation Patients receiving thiopurines for inflammatory bowel disease have an increased risk of developing lymphoproliferative disorders.

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Introduction

Crohn's disease and ulcerative colitis (collectively referred to as inflammatory bowel disease) are chronic inflammatory gastrointestinal disorders of unknown origin. The thiopurine azathioprine and its metabolite, 6-mercaptopurine, are used for their immunosuppressive properties to maintain remission in these disorders.[1,2] They are recommended in various forms of chronic clinically active inflammatory bowel disease, including steroid-dependent forms.[3] Organ transplant recipients receiving these drugs as part of their immunosuppressive therapy are at an increased risk of developing lymphoproliferative disorders,[4] with a frequent pathogenic association with Epstein-Barr virus.[5] No excess risk of lymphoproliferative disorder has been shown in large population-based studies of patients with inflammatory bowel disease,[6,7] but conflicting data have been reported for patients given thiopurines.[8–10] In view of the increasing use of these drugs as maintenance treatment of inflammatory bowel disease, and the availability of alternative maintenance treatments,[11–13] settlement of this issue by means of prospective studies is important. We therefore initiated a nationwide prospective observational cohort, called CESAME (Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France), which was designed mainly to assess the possible excess risk of lymphoproliferative disorder in patients with inflammatory bowel disease receiving thiopurines.

Methods

Study design

In this prospective cohort study, the incidence rates of lymphoproliferative disorder were compared in patients treated and not treated with thiopurines during a 3-year follow-up. We also compared reported cases of lymphoproliferative disorder in the cohort with the number of cases expected in the general population with the same age and sex distributions.

Patients with inflammatory bowel disease were recruited to the study from May, 2004, to June, 2005. Follow-up ended on Dec 31, 2007. From January to April, 2004, all 4171 gastroenterologists and paediatricians on the mailing

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	Continuing (n=5867)	Discontinued (n=2809)	Never received (n=10 810)	Total (n=19 486)
Age (years)	37·0 (14·3)	39·5 (14·4)	42·3 (16·3)	40·3 (15·6)
Male sex	2592 (44%)	1142 (41%)	5046 (47%)	8780 (45%)
Age at onset of disease (years)	28·6 (13·2)	29·0 (13·4)	34·9 (15·1)	32·1 (14·6)
Duration of disease (years)	8·4 (7·2)	10·5 (7·8)	7·4 (8·4)	8·2 (8·0)
Crohn's disease	4452 (76%)	2154 (77%)	5153 (48%)	11 759 (60%)
Disease site				
Ileum	3082 (53%)	1543 (55%)	3597 (33%)	8222 (42%)
Colon (<50%)*	1358 (23%)	627 (22%)	1876 (17%)	3861 (20%)
Colon (>50%)	2079 (35%)	1085 (39%)	1426 (13%)	4590 (24%)
Perianal	1384 (24%)	740 (26%)	787 (7%)	2911 (15%)
Ulcerative colitis or unclassified inflammatory bowel disease	1415 (24%)	655 (23%)	5657 (52%)	7727 (40%)
Colon (<50%)*	578 (10%)	237 (8%)	3883 (36%)	4698 (24%)
Colon (>50%)	837 (14%)	418 (15%)	1774 (16%)	3029 (16%)
Methotrexate therapy				
Continuing	0 (0%)	653 (23%)	41 (<1%)	694 (4%)
Discontinued	219 (4%)	458 (16%)	22 (<1%)	699 (4%)
Never received	5648 (96%)	1698 (61%)	10 747 (99%)	18 093 (93%)
Therapy against TNFα				
Continuing	543 (9%)	322 (12%)	60 (<1%)	925 (5%)
Discontinued	504 (9%)	475 (17%)	35 (<1%)	1014 (5%)
Never received	4820 (82%)	2012 (72%)	10 715 (99%)	17 547 (90%)
Other immunosuppressants†				
Continuing	74 (1%)	61 (2%)	62 (<1%)	197 (1%)
Discontinued	202 (3%)	220 (8%)	58 (<1%)	480 (3%)
Never received	5591 (95%)	2528 (90%)	10 690 (99%)	18 809 (97%)
History of cancer	83 (1%)	77 (3%)	302 (3%)	462 (2%)
History of LD	3 (<1%)	8 (<1%)	12 (<1%)	23 (<1%)
Follow-up (months)	35·7 (31·1–40·1)	35·4 (29·9–40·0)	34·3 (27·7–39·1)	35·0 (29·2–39·5)

Data are mean (SD), number (%), or median (IQR).TNF=tumour necrosis factor; LD=lymphoproliferative disorder. *Estimated cumulative proportion of mucosal area macroscopically or microscopically affected. †Ciclosporin, mycophenolate mofetil, or cyclophosphamide.

Table 1: **Patient characteristics by thiopurine status at entry**

list of the yearly French national gastroenterology meeting were sent a letter asking them to participate in the CESAME study on a voluntary and unpaid basis: 817 practitioners located throughout France agreed to participate (roughly a third of active French gastroenterologists treating inflammatory bowel disease). 320 (39%) participants were in full-time hospital practice, 200 (24%) mixed public/private practice, and 297 (36%) full-time private practice. They were asked to enrol all consecutive patients with a diagnosis of inflammatory bowel disease seen for any reason during the first year of the study. A 1-year inclusion period was chosen because in France patients with stable inflammatory bowel disease are seen by their gastroenterologist at least once a year, and usually twice, since the maximum validity period for prescriptions is 6 months. There were no exclusion criteria.

Data were obtained on an electronic case-report form. The patients' demographic characteristics, type of inflammatory bowel disease, date of diagnosis, cumulative disease location, previous history of cancer, and exposure to immunosuppressive therapy were recorded at inclusion in the cohort. Participants were asked to report all cases of cancer or death in their patients during follow-up, and to provide information for each patient (apart from those who died) obtained during a final visit that took place between Jan 1, and Dec 31, 2007. They were also asked to record all changes in immunosuppressive therapy status at interim visits. A specific case report form was used for patients with a history of lymphoproliferative disorder and for those who developed the disorder during follow-up. Clinical data for inflammatory bowel disease were reviewed by a senior gastroenterologist (LB) and those for lymphoproliferative disorder were reviewed by a senior haematologist (OH). Biopsy and surgical specimens were centralised in Hôpital Necker-Enfants Malades for a second expert review (NB) after examination in primary-care pathology departments. The 2008 WHO classification of lymphoproliferative disorder was used.[14] Epstein-Barr virus status was recorded as positive if the virus' proteins or RNA were detected in neoplastic tissues.

Onset was defined as the date of the first symptoms attributable to lymphoproliferative disorder—for instance, clinical observation of adenopathies (which can be retrospectively attributed to the disorder after histological confirmation) and neurological manifestations revealing brain lymphoma. Incident cases of lymphoproliferative disorder were defined as those occurring after inclusion in the cohort. To avoid selection bias, patients who had symptoms attributable to the disorder at inclusion in the study were not considered as incident cases in the main analysis. We also excluded cases occurring in patients in whom the disorder had been diagnosed during the 5 years before inclusion, to avoid mistaking early recurrences for new incident cases (none occurred).

Data for incidence of lymphoproliferative disorder in the general population were obtained from the Association of French Cancer Registries, which gathers data from 20 population-based regional cancer registries. Data for inflammatory bowel disease activity were available for a subset of patients in the cohort who were also enrolled in the Saint-Antoine hospital clinical database.[15] These patients had a prospective yearly assessment of their clinical inflammatory bowel disease activity (classified as active or inactive).

The protocol was approved by the institutional review boards of the French National Society of Gastroenterology, Association François Aupetit (the French patient association for inflammatory bowel disease), and Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif. We obtained authorisation from the French Data Protection Agency (CNIL, registration number #04-1239). Specific written informed patient consent was not needed for this observational study.

Statistical analysis

We estimated that a minimum of 50 000 person-years of follow-up would be needed for the study to have statistical power of 80% to detect an lymphoproliferative disorder hazard ratio (HR) of at least 3·5 in patients given thiopurines relative to patients not given these drugs, assuming an absolute incidence rate of 20 cases per 100 000 person-years in untreated patients and that 40% of patients with inflammatory bowel disease would be exposed to thiopurines.

Patients were excluded from all analyses if they were enrolled by an investigator who subsequently declined to participate further (99 investigators), or who died (four), retired (seven), or moved to a different practice (27). Baseline characteristics were compared according to thiopurine exposure by the χ^2 and Kruskal-Wallis tests. The main outcome measure was the rate of incident lymphoproliferative disorder. We used a Cox regression model in which treatment was introduced as a time-dependent covariate to quantify strength of associations between thiopurine exposure and outcome. We distinguished patients who never received thiopurines from those who had discontinued thiopurines and those receiving thiopurines. For periods between the entry visit and an interim visit, or between two interim visits, changes in thiopurine exposure were assumed to have occurred during the visit with a change reported, and exposure status during the relevant period was assumed to be the same as at the start of the period (never received, discontinued, or continuing). For periods ending with the final visit, or in case of death or onset of lymphoproliferative disorder, changes in treatment were judged to have occurred at an unknown date during the period and were imputed to the midpoint of that period.[16]

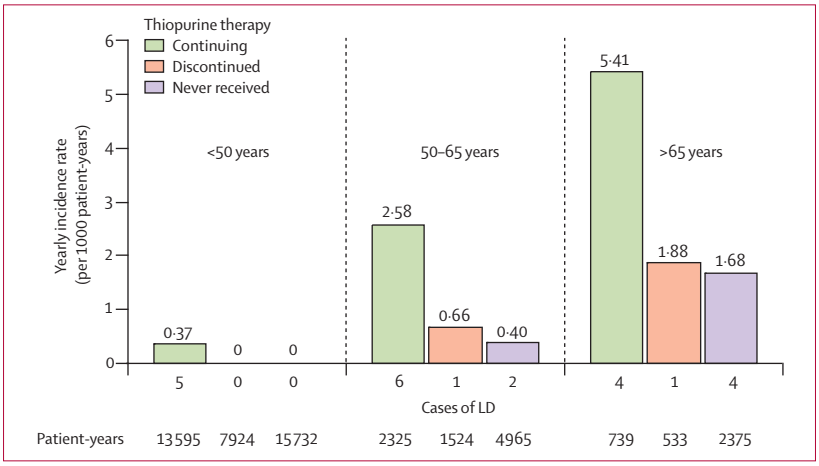

Figure: **Incidence rates of lymphoproliferative disorders according to thiopurine exposure grouped by age at entry in the cohort**
LD=lymphoproliferative disorder.

A constant hazard for risk of lymphoma in patients exposed to thiopurines has been clearly established in the post-transplant setting.[17,18] We therefore regarded risk of lymphoma as constant in patients exposed to thiopurines, irrespective of the (unrecorded) duration of treatment before study entry, and the effect of thiopurines was assumed to start at the first treatment intake and to stop on cessation. We built a multivariate-adjusted regression model in which potential confounders were tested separately in a univariate Cox regression model, and significant confounders were selected to be entered in the multivariate model. Note that the small expected number of lymphoproliferative disorder events prevented us from including more than four or five covariates in the final multivariate model.[19] We used conventional methods to test a departure from the proportional-hazards assumption that the effect exerted on the hazard by a time-non-dependent variable selected in the multivariate model was constant in time.[20] We also did many sensitivity analyses to detect possible biases (see webappendix).

For graphical representations, age at entry in the cohort was grouped as less than 50 years, 50–65 years, and older than 65 years. The expected number of cases of lymphoproliferative disorder in the general population was obtained by multiplying the patient-years at risk in

See Online for webappendix

	Hazard ratio (95% CI)	p value
Age (per 1-year increase)	1·06 (1·03–1·09)	<0·0001
Duration of inflammatory bowel disease (per 1-year increase)	1·04 (1·00–1·08)	0·0359
Sex		
Female*	..	..
Male	2·32 (0·95–5·64)	0·0648
Thiopurine therapy†		
Never received*	..	..
Discontinued	1·02 (0·20–5·11)	0·9839
Continuing	5·28 (2·01–13·9)	0·0007

*Reference group. †Time-dependent thiopurine therapy was coded with two dummy variables: continuing therapy was equal to zero when thiopurines were not used, and one from the start of therapy to discontinuation (if any); discontinued therapy was equal to zero when thiopurines were used or if thiopurines were never used, and one from treatment interruption to reintroduction (if any). The hazard ratio between patients with continuing thiopurine therapy (or patients who discontinued therapy) and patients who had never received thiopurines represents the relative risk for an individual on therapy (or who has discontinued therapy) compared with a never-treated individual.

Table 2: **Independent risk factors for lymphoproliferative disorder**

each 5-year age group by the corresponding sex-specific and age-specific incidence rate for 2005, provided by the French Cancer Registries database (FRANCIM). The reported number of cases of lymphoproliferative disorder was divided by the expected number to obtain a standardised incidence ratio estimate. CIs for rates and standardised incidence ratios were calculated with an exact method based on the Poisson distribution.[21]

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had responsibility for the decision to submit for publication.

Results

20 775 patients were enrolled in the study. Of these, 19 486 patients (94%) were included in all analyses because they were enrolled by investigators who continued to participate in the study. Follow-up was complete (ie, included a final visit) for 16 459 of these patients (85%), part complete (interim visits but no final visit) for 588 (3%), and non-existent for 2439 (13%). At study entry, 5867 (30%) patients were receiving thiopurines, 2809 (14%) had discontinued thiopurines, and 10 810 (56%) had never received thiopurines. Compared with patients who never received thiopurines, those who did so were younger (p<0·0001), more frequently women (p=0·0020), and more likely to have Crohn's disease (p<0·0001); they also had a longer duration of inflammatory bowel disease (p<0·0001), and were less likely to have had cancer (p<0·0001) (table 1). Patients who, at study entry, had previously received thiopurines resembled those who were receiving these drugs—they were more likely to be younger women and to have Crohn's disease, and had longer disease duration than did patients who never received thiopurines (p<0·0001 for all comparisons).

During the study, 114 (2%) patients receiving thiopurines at study entry, 41 (1%) patients who had discontinued these drugs, and 134 (1%) patients who had never received them developed cancer (p=0·0016 for comparison of proportions). 46 (<1%) patients receiving thiopurines at study entry, 45 (2%) of those who had discontinued thiopurines, and 95 (<1%) of those who had never received thiopurines died (p<0·0006), of whom 16, eight, and 31 (all <1%), respectively, died of cancer (p=0·9864).

During 49 713 patient-years of follow-up, 23 patients were diagnosed with incident lymphoproliferative disorder by 22 investigators (one case of Hodgkin's lymphoma and 22 cases of non-Hodgkin lymphoproliferative disorder). Of these 23 patients, 15 (including the patient with Hodgkin's lymphoma) were receiving thiopurines at symptom onset, two had discontinued thiopurine therapy, and six had never received thiopurines. Nine patients were diagnosed with the disorder occurred during the first year of follow-up, five the second year, and nine beyond the second year. The incidence rates were 0·90 per 1000 (95% CI 0·50–1·49) patient-years in those receiving; 0·20 per 1000 (0·02–0·72) patient-years in those who discontinued; and 0·26 per 1000 (0·10–0·57) patient-years in those who never received thiopurines (p=0·0054 for comparison of rates). The unadjusted HRs were 3·45 (1·34–8·89, p=0·0106) for patients who received versus those who never received thiopurines and 0·74 (0·15–3·68, p=0·7094) for patients who discontinued thiopurines versus those who never received these drugs. The unadjusted HR was 3·75 (1·59–8·85, p=0·0025) for patients who received thiopurines versus all other patients.

Pre-planned exploratory analyses identified old age (see figure), male sex, and longer duration of inflammatory bowel disease (table 2) as factors associated with risk of incident lymphoproliferative disorder. Multivariate HR analysis adjusted for different risk factors substantiated the independent association between continuing thiopurine therapy and risk of lymphoproliferative disorder (table 2). The multivariate-adjusted HR between patients who received thiopurines and all other patients was 5·26 (2·20–12·6, p=0·0002). Findings were consistent across sensitivity analyses (see webappendix). Table 3 shows standardised incidence ratios. We saw no increase in patients with lymphoproliferative disorder in those who never received thiopurines relative to the general population, during 23 073 patient-years of follow-up.

Disease activity between 2004 and 2007 was available for the subset of 1347 patients who were also enrolled in the Saint-Antoine hospital clinical database. We showed that the proportion of follow-up during which

inflammatory bowel disease was clinically active did not differ between the 496 patients who were receiving thiopurines at entry (active for 30·6% of follow-up) and the 642 who never received such treatment (33·0%, p=0·3649), but that it was smaller than in the 209 patients who discontinued thiopurines (37·2%, p=0·0401).

Table 4 shows clinical and pathological data for incident lymphoproliferative disorder. Of the eight patients who were not receiving thiopurines at symptom onset, only one had post-transplant lymphoproliferative disorder, according to WHO classification. Of the 15 patients who were receiving immunosuppressive therapy at the time of symptom onset, 12 had post-transplant-type lymphoproliferative disorder. The gastrointestinal tract was affected in six cases. Eight patients died from causes related to the disorder within the study period. We noted two cases of fatal early postmononucleosis lymphoproliferative disorder in young men but none of T-cell hepatosplenic lymphoma.

	Patient-years	Reported cases	Expected cases	Standardised incidence ratio	95% CI	p value
Thiopurine therapy						
Continuing	16659	15	2·19	6·86	3·84–11·31	<0·0001
Discontinued	9981	2	1·39	1·44	0·17–5·20	0·8095
Never received	23073	6	4·19	1·43	0·53–3·12	0·4900
Anti-TNFα therapy						
Continuing	4128	2	0·44	4·53	0·55–16·4	0·1462
Discontinued	3667	3	0·43	6·92	1·43–20·2	0·0197
Never received	41918	18	6·89	2·61	1·55–4·13	<0·0001
Continuing thiopurine therapy and continuing anti-TNFα therapy	1929	2	0·20	10·2	1·24–36·9	0·0337
Continuing thiopurine therapy and discontinued or never received anti-TNFα therapy	14729	13	1·99	6·53	3·48–11·2	<0·0001
Never received thiopurine therapy or anti-TNFα therapy	22706	6	4·13	1·45	0·53–3·16	0·4711

TNF=tumour necrosis factor. *Lymphoproliferative disorder did not arise in patients given methotrexate.

Table 3: **Standardised incidence ratios of lymphoproliferative disorder according to thiopurine therapy and anti-TNFα therapy at clinical onset***

Discussion

We have shown that risk of lymphoproliferative disorder was five times higher in patients exposed to thiopurines than in those never exposed to these drugs. Old age, male sex, and longer duration of inflammatory bowel disease were also associated with increased risk of incident lymphoproliferative disorder.

Our hypothesis of a constant risk of lymphoproliferative disorder during thiopurine therapy is supported by three considerations. First, in the post-transplant setting the risk of lymphoma is constant provided that a consistent dose of immunosuppressants is given. Second, we recorded the same number of incident lymphomas in the first and third years of the observation period. Third, the duration of previous thiopurine exposure was evenly distributed among the 23 patients who developed lymphoma. Duration of thiopurine therapy before study entry and doses given were not recorded for patients in the CESAME database, thus we cannot test the effect of cumulative exposure or acute high doses on risk of lymphoproliferative disorder. However, constant daily doses are recommended worldwide, and in this context, acute exposure to high doses of thiopurines can only be brief and accidental, and is not relevant to the overall patient population.

Most of the limitations of our study were addressed by sensitivity analyses. In particular, to rule out bias due to the absence of follow-up data for almost 13% of patients, we showed that the increased risk of lymphoproliferative disorder in those receiving thiopurines remained significant when we simulated the possibility that patients with missing follow-up data who were thiopurine-naive at inclusion in the cohort had the same risk as patients who received thiopurines during the observation period, and vice versa. To support the relevance of our case-definition of incident lymphoproliferative disorder, which excluded patients with possible symptoms of the disorder at inclusion in the cohort, we showed that magnitude of the incidence rates did not change during the last third of the observation period. To explore possible bias due to the small number of incident lymphoproliferative disorder events, we did a nested case-control analysis matched on the propensity score and on other potential confounders and showed that the odds ratio estimated with an exact method between patients who received thiopurines and all other patients was in line with our main findings.

The excess risk of lymphoproliferative disorder in patients receiving thiopurines for chronic inflammatory diseases might be due to the inflammatory process itself, or to thiopurine exposure, or to a combination of the two.[6,9,22] In rheumatoid arthritis, results of several epidemiological studies suggest that the subset of patients with the most severe uncontrolled inflammation have a substantially increased risk of lymphoproliferative disorder, irrespective of exposure to thiopurines.[23] We show that duration of inflammatory bowel disease is an independent risk factor for lymphoproliferative disorder. Because this risk is likely to be related to uncontrolled chronic inflammation, the question arises, are patients with uncontrolled inflammation over-represented in the group receiving thiopurines? We cannot directly answer this question. First, however, thiopurines induce and maintain clinical remission in a substantial proportion of patients and can induce mucosal healing.[24]

Second, since the early 2000s, use of thiopurines has not been restricted to the most severely ill patients.[25] Third, patients who discontinued thiopurine therapy in our study had a similar risk to patients who never received thiopurines. Fourth, in a subset of patients we noted that the mean duration of clinically active inflammatory bowel

	Age (year)*	Sex	Type of IBD	Organ	Type of LD	Immunosuppressive therapy*	Exposure to AZA/6-MP (year)	EBV status
Patients naive to immunosuppressive therapy at clinical onset of LD								
1	54	M	CD	Lymph nodes	B follicular lymphoma	..	..	–
2	67	M	UC	Lymph nodes	B follicular lymphoma	..	..	..
3†	69	M	UC	Lymph nodes	B follicular lymphoma	..	..	–
4	75	F	UIBD	Skull/bone marrow	Diffuse large B-cell LD	..	..	..
5	76	M	CD	Lymph nodes	T-cell lymphoma AIL-type	..	..	+
6	80	M	CD	Small bowel	Diffuse large B-cell LD	..	..	+
Patients previously given immunosuppressive therapy at clinical onset of LD								
7‡	75	F	UC	Thorax	Diffuse large B-cell LD	..	..	..
8§	56	M	CD	Small bowel	Diffuse large B-cell LD	..	..	–
Patients receiving immunosuppressive therapy at clinical onset of LD								
9	20	M	CD	Small bowel	Early postmononucleosis B-LD	AZA¶	3	+
10	22	F	CD	Lymph nodes	Anaplastic large cell LD	AZA||	1	–
11	25	F	CD	Lymph nodes	Hodgkin's lymphoma	6-MP**	8	+
12	26	M	CD	Lymph nodes	Early post-MNI B-LD	AZA	4	+
13	37	F	CD	Disseminated	Polymorphic B LD	AZA	3	+
14	42	M	CD	Lung/liver	B-LD Hodgkin-like	AZA	16	+
15	54	F	CD	Lymph nodes	Polymorphic B LD	AZA	3	+
16	55	F	CD	Small bowel	Immunoblastic large B-cell lymphoma	AZA††	13	–
17	56	M	CD	Lymph nodes	B follicular lymphoma	AZA	1	–
18	60	M	UC	Brain	Polymorphic B LD	AZA	2	+
19	60	M	CD	Rectum	Diffuse large B-cell LD	AZA+IFX‡‡	3	+
20	76	M	CD	Lymph nodes/abdomen	T-cell LD	AZA+IFX§§	5	+
21	78	M	UC	Bone marrow	Plasmacytic B LD	AZA	10	..
22	79	M	UC	Brain	Polymorphic B LD	AZA	9	+
23	79	F	CD	Colon	Unclassifiable	AZA	7	–

IBD=inflammatory bowel disease. LD=lymphoproliferative disorder. AZA=azathioprine. MP= mercaptopurine. EBV=Epstein-Barr virus. M=male. CD=Crohn's disease. UC=ulcerative colitis. F=female. UIBD=unclassified inflammatory bowel disease. AIL=angioimmunoblastic lymphoma. IFX=infliximab. *At clinical onset of LD. †This patient had a history of LD 11 years before study entry. ‡1-year treatment with azathioprine, stopped 13 months before clinical onset of LD. §10-year treatment with azathioprine, stopped 6 months before clinical onset of LD. ¶Additional 1-year treatment with infliximab, stopped 36 months before clinical onset of LD. ||Additional 2-month treatment with ciclosporin, stopped 11 months before clinical onset of LD. **Additional 2-month treatment with infliximab, stopped 11 months before clinical onset of LD. ††Additional 5-month treatment with infliximab, stopped 17 months before clinical onset of LD. ‡‡1-year exposure to infliximab. §§4-year exposure to infliximab.

Table 4: **Characteristics of incident cases of lymphoproliferative disorder**

disease during follow-up was similar in those who had never been exposed to thiopurines and in those who received thiopurines; additionally, inflammatory bowel disease was more clinically active and risk of lymphoproliferative disorder was lower in patients who discontinued thiopurine therapy than in those receiving thiopurines. This finding strongly suggests that the excess risk of lymphoproliferative disorder seen in patients given thiopurines is more likely to be related to the immunosuppressive effects of thiopurines than to over-representation of chronic inflammation in patients receiving thiopurines.

Most cases of lymphoproliferative disorder reported in patients given thiopurines were post-transplant lymphoproliferative disorder-like B-cell disorders and were associated with Epstein-Barr virus, suggesting a major role of immunosuppression in both settings. Thiopurines are cytotoxic for natural killer and cytotoxic T cells, which restrict proliferation of Epstein-Barr virus-infected and immortalised B cells.[26,27] This process could be the main mechanism of lymphomagenesis in patients receiving thiopurines and warrants prospective studies to establish whether the gradual increase in Epstein-Barr virus load or the decline in the cytotoxic T-lymphocyte count and ex vivo T-cell cytotoxicity for virus-infected cells could serve as predictors for lymphoproliferative disorder in patients with inflammatory bowel disease given thiopurines.

We recorded two cases of early fatal postmononucleosis lymphoproliferative disorder in young men receiving thiopurines, suggesting a harmful combined effect of genetic susceptibility, as in X-linked lymphoproliferative disorder,[28] and thiopurine immunosuppression.[29] This risk, although low (1 in 10 000), should be known when thiopurine therapy is being considered for young Epstein-Barr virus-seronegative patients. As in a previous retrospective series of lymphoproliferative disorder in patients with inflammatory bowel disorder,[8] we noted several cases of intestinal lymphoproliferative disorder, often arising in intestinal segments involved in

inflammatory bowel disease and often associated with Epstein-Barr virus. This finding suggests that lymphoproliferative disorders might, like adenocarcinoma,[30] be a potential local complication of chronic inflammation of intestinal mucosa. Such inflammation-related lymphoproliferative disorders (mostly associated with the Epstein-Barr virus) have previously been described in patients with chronic pleural inflammation.[31] Finally, although there were few children and adolescents in our cohort, we saw no cases of T-cell hepatosplenic lymphoma, confirming that this particular risk is very low.

Whether the risk of lymphoproliferative disorder is also increased in patients receiving immunosuppressants other than thiopurines is not yet known. No increase in risk of lymphoproliferative disorder has been reported in patients receiving methotrexate for rheumatoid arthritis,[32] but use of methotrexate in inflammatory bowel disorder is too restricted to assess this risk. In our study, few patients were given tumour necrosis factor inhibitors and most of them also received thiopurines, so we are unable to draw conclusions about this therapeutic class. Extrapolating our results, the absolute cumulative risk of lymphoproliferative disorder in young patients receiving a 10-year course of thiopurines remains low (<1%) and does not undermine the positive risk-benefit ratio of these drugs.[33] For elderly patients and unlimited treatment periods, the question should be addressed in dedicated studies.

Contributors

LB and FC were jointly responsible for the study idea, design, and implementation, and they produced jointly the first draft of the report. FC was responsible for all statistical and sensitivity analyses. NB was responsible for the central collection and review of histological data and was a member of the steering committee. AMB, MM, and JF were responsible for providing data extracted from cancer registries and for calculation of expected cases of lymphoproliferative disorder; they were also members of the steering committee. JFC and ML were involved in study conception, were members of the steering committee, and were two of the six investigators who included the greatest numbers of patients. JC was responsible for data on clinical activity of inflammatory bowel disease and was one of the six investigators who included the greatest number of patients. XH, AC, and YB were three of the six investigators who included the greatest numbers of patients. JPG was a member of the steering committee and one of the six investigators who included the greatest numbers of patients. TS was involved in the design and implementation of collection of endpoint data. OH was involved in the review of clinical data for lymphoproliferative disorder. All authors took part in the revision of the report.

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Conflicts of interest

LB received funding from UCB Pharma for advisory activity, as a member on an advisory board, from Sanofi-Aventis for technical expertise, Abbott for an educational activity, and Ferring Pharmaceuticals as an unconditional grant for sponsoring the case-control study on risk factors of CRC in inflammatory bowel disease, nested in the CESAME cohort. JFC declared consulting fees or paid advisory boards for Abbott Laboratories, ActoGeniX NV, AstraZeneca, Berlex, Boehringer Ingelheim, Bristol-Myers Squibb, Cellerix SL, Chemocentryx, Centocor, Cosmo Technologies, Danone France, Elan Pharmaceuticals, Genentech, Giuliani SPA, Given Imaging, GlaxoSmithKline, Millenium Pharmaceuticals, Neovacs SA, Ocera Therapeutics, Otsuka American Pharmaceuticals, PDL Biopharma, Pfizer, RiboVax Biotech, Schering-Plough Corporation, Shire Pharmaceuticals, Synta Pharmaceutical Corporation, Teva Pharmaceuticals, Therakos, UCB Pharma, and Wyeth Pharmaceuticals, received lecture fees from speaking at continuing medical education events indirectly sponsored by a commercial sponsor from Abbott Laboratories, AstraZeneca, Centocor, Elan Pharmaceuticals, Falk Pharma, Ferring, Given Imaging, Otsuka American Pharmaceuticals, PDL Biopharma, Schering-Plough Corporation, Shire Pharmaceuticals, and UCB Pharma, and grant support from Abbott Laboratories, AstraZeneca, Ferring, Schering-Plough Corporation, UCB Pharma, and owns stock in Intestinal Biotech Development. ML declared consulting fees from Abbott, Schering-Plough, UCB Pharma, Ferring, and AstraZeneca. XH received funding from UCB Pharma for advisory activity, as a member on an advisory board, and from Abbott for educational activities. AC received consulting fees from Ferring France, AstraZeneca France,

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