Journal of Crohn's and Colitis (2013) 7, 385–391

Available online at www.sciencedirect.com

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The risk of lymphoma and immunomodulators in patients with inflammatory bowel diseases: Results from a population-based cohort in Eastern Europe

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Received 18 March 2012; received in revised form 17 May 2012; accepted 11 June 2012

KEYWORDS
IBD;
Lymphoma;
Incidence;
Standardized incidence ratio

Abstract

Background and aims: Prior studies suggest a small but significantly increased risk of lymphoma in adults with inflammatory bowel disease (IBD), especially in patients treated with thiopurines. No data was available from Eastern Europe. The aim of this study was to analyze the incidence of lymphomas as related to drug exposure, in a population-based Veszprem province database, which included incident cases diagnosed between January 1, 1977 and December 31, 2008.
Methods: Data from 1420 incident patients were analyzed (UC: 914, age at diagnosis: 36.5 years; CD: 506, age at diagnosis: 28.5.5 years). Both in- and outpatient records were collected and comprehensively reviewed. The rate of lymphoma was calculated as patient-years of exposure per medication class, of medications utilized in IBD.

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1873-9946/$ - see front matter
doi:10.1016/j.crohns.2012.06.011

Results: Of the 1420 patients, we identified three patients who developed lymphoma (one CLL, two low-grade B-cell NHL including one rectal case), during 19,293 patient-years of follow-up (median follow-up: 13 years). All three patients were male. None had received azathioprine or biologicals. The absolute incidence rate of lymphoma was 1.55 per 10,000 patient-years, with 3 cases observed vs. 2.18 expected, with a standardized incidence ratio (SIR) of 1.37 (95% confidence interval [CI]: 0.44–4.26). No cases have been exposed to either azathioprine or biologicals.

Conclusions: The overall risk of lymphoma in IBD was not increased; only three cases were seen in this population-based incident cohort over a 30-year period. An association with thiopurine exposure was not found.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders with increasing incidence and prevalence. CD may involve any part of gastrointestinal tract, and is characterized by ulcerations and transmural inflammation that may produce complications, including bowel strictures or fistulas; whereas in UC the inflammatory process is restricted to the colon.[1,2] Current therapeutic modalities have changed significantly over the last decades, with more widespread and earlier use of biologicals and immunomodulator agents (e.g. azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]). There exists increasing evidence that the change in treatment is associated with a change in the natural history of the disease.[3] In contrast, available evidence may suggest a possible link between IBD, immunomodulator therapy and tumor risk, including risk for colorectal cancer[4,5] and lymphoma.

The incidence of malignant lymphomas has increased recently worldwide in recent years. In the United States, NHL now represents the fifth most commonly occurring cancer, with an incidence of 19 per 100,000 people annually. NHL appears more often in Caucasians than in Afro-Caribbeans, and affects males more frequently.[6] Lymphomas that develop in IBD are heterogeneous. Generally, lymphomas can be divided into non-Hodgkin's lymphoma (90% of lymphomas) and Hodgkin's lymphoma (10% of lymphomas). The risk of lymphoma in IBD patients may be associated with two main factors: the inflammatory process itself and the widespread use of immunomodulators for prolonged periods. Inflammation has been reported as a risk factor for neoplasm in patients with RA.[7,8] In a Swedish RA cohort, authors detected a 70-fold increase in lymphoma risk in patients with high disease activity, suggesting that the disease activity itself, rather than the therapy, can be a risk factor for lymphomatous transformation. The same was reported also in IBD.[9] Nonetheless, it has been shown that immunomodulators can increase the risk of lymphoma in AIDS and transplantation recipients[10] as well. Some therapeutic modalities, such as alkylating agents and MTX, are risk factors of lymphoma in RA, but only a fraction of lymphomas can be attributed to the carcinogenic effects of these drugs. Similar considerations should be applied for cyclophosphamide, chlorambucil, AZA, and other conventional immunomodulator medications.

In most population based studies IBD itself does not appear to be associated with an increased risk of lymphoma.[11–15] In one of the early reports by Lewis et al.,[11] the incidence of lymphoma was not elevated in CD (RR: 1.39) or UC (RR: 1.11), as compared to controls. In contrast, Bernstein et al.[16] reported that incidence rates and rate ratios of lymphoma were increased for males with CD only (3.63; 95% CI: 1.53–8.62). A potential deleterious role for immunosupressives was also suggested by the meta-analysis by Kandiel et al.,[17] where the pooled relative risk of lymphoma in CD patients treated with immunomodulators (AZA or MTX) was 4.18 (95% CI: 2.47–7.51). Increased risk of lymphoma was thought to be due to medication, disease severity, or a combination of the two. In addition, the risk of lymphoma was reported to be increased in the CESAME study.[18] At baseline, 30.1% of patients had current immunomodulator therapy, while 10.0% had discontinued immunosuppressants, and 55.5% were immunosuppressant-naïve. One case of Hodgkin disease and 22 cases of NHL were reported. The multivariate-adjusted hazard ratio of lymphoproliferative disorders in patients receiving thiopurines versus those who had never received the drugs was 5.28 (2.01–13.9, $p=0.0007$). The same researchers reported recently that the risk for primary intestinal lymphoproliferative disorders was increased in patients with IBD.[19] The reported standardized incidence ratio was 17.5 (95% CI: 6.4–38.1) and risk was highest in patients exposed to thiopruines (SIR: 49.4; 95% CI: 13.5–126.8).

In contrast, there are no published studies that rigorously investigated the risk of lymphoma in IBD patients treated with MTX. The potential association was examined indirectly in the hospital-based study by Farrell et al.,[20] where 2 of 31 MTX exposed patients developed NHL. Of note, one of these patients who developed NHL was also exposed to cyclosporine. Finally, in a meta-analysis by Siegel et al. the risk of lymphoma was reported to be increased in patients with previous immunomodulator exposure who were currently receiving anti-TNF agents (SIR: 3.23, 95% CI: 1.5–6.9).[21]

Since previous studies suggest a small but significantly increased risk of lymphoma in adults with inflammatory bowel disease (IBD) treated with thiopurines, and as no data are available from Eastern Europe, this study was undertaken to analyze the incidence of non-Hodgkin lymphoma in relation to drug exposure in a population-based Veszprem province database, which included incident patients diagnosed between January 1, 1977 and December 31, 2008.

2. Patients and methods

2.1. Study population

A well-characterized Hungarian cohort of 1420 incident cases with inflammatory bowel diseases diagnosed between January 1, 1977 and December 31, 2008 were included. In total, 914 ulcerative colitis (UC, male/female: 479/435, median age at diagnosis: 36.5 years) and 506 Crohn's disease (CD, male/female: 251/255, median age at diagnosis: 28.5 years) patients were diagnosed during the inclusion period. Patient follow-up was continued until December 31, 2010 or until death. Patients with indeterminate colitis (IC) at diagnosis were excluded from the analysis. The clinical data of CD patients is summarized in Table 1. Veszprem province is located in western Hungary. The province consists of both industrial and agricultural regions. The permanent population was relatively stable in number, with a slight decrease from 376,000 to 364,500 from 1990 to 2006. The Roma population is underrepresented as compared with Hungary overall (2.5%), while few people of Jewish ancestry live in the province. The ratio of urban/rural was also relative stable (55% urban). For the purposes of statistical analysis, national incidence rates of Hodgkin's disease and non-Hodgkin lymphoma were obtained from the National Cancer Registry (NCR),[22] while age- and gender-specific demographic data of the province was obtained from the Hungarian Central Statistical Office (KSH).

Table 1 Clinical characteristics of patients with IBD.

	CD	UC
	n = 506	N = 914
Male/female	251/255	479/435
Age at presentation (years) [a]	28.5, range: (22–38)	36.5 (26.5–51)
Follow-up (years) [a]	13, range: (6–19.5)	13 (7.5–20)
Familial IBD	12.9%	7.7%
Location		
L1	32.8%	-
L2	35.9%	
L3	30.6%	
L4 only	0.7%	
Extent at diagnosis	-	
Proctitis		25.4%
Left-sided		50.2%
Extensive		24.4%
Proximal extension		
At 5 years	-	8.8%
At 10 years		13.0%
At the end of follow-up		16.1%
Behavior at diagnosis		
B1	56.9%	-
B2	19.8%	
B3	23.3%	
Frequent relapse	13.1%	5.6%
Perianal disease	25.5%	-
Arthritis	26.7%	13.3%
PSC	1.8%	2.7%
Ocular	4.7%	2.8%
Cutaneous	9.3%	2.5%
Steroid use	68.6%	38.6%
Azathioprine use	45.8%	7.4%
Biological use	10.7%	1%
Resection/re-operation	41.3%/28.2%	4.2%
Colectomy in UC		
Smoking habits		
at diagnosis		
no	44.6%	67.5%
ex	7.2%	17.6/
yes	48.2%	14.9%

[a] median (IQR).

IBD patient data were collected every year from the seven general hospitals (internal medicine, surgery, and pediatric departments) and gastroenterology outpatient units, each staffed by at least one gastroenterologist or internist with special interest in gastroenterology, as well as family physicians. The majority of patients (94% of CD and 76% of UC patients) were monitored at the Csolnoky Ferenc Province Hospital in Veszprem. This hospital also serves as a secondary referral center for IBD patients in that province. Data collection was prospective since 1985, while prior to 1985, only in the city of Veszprem was data collected prospectively. In other sites throughout the province, data for this period (1977–1985) were collected retrospectively in 1985. Both in- and outpatients permanently residing in the area were included in the study. Diagnoses, based on hospitalization records, records of outpatient visits, as well as records of endoscopic, radiological and histological examinations performed at participating centers were reviewed thoroughly, using the Lennard–Jones criteria.[23] The provincial IBD register data were centralized in Veszprem. Disease phenotype was assessed by a questionnaire completed by the clinician at the time of diagnosis and updated yearly, as necessary. A more detailed description of our data collection method, case assessment, geographical and socioeconomic statistics for the province, and a description of the Veszprem Province IBD Group were published in our previous epidemiological studies.[2,4]

Age, age at onset, family history of IBD, the presence of extraintestinal manifestations (EIM: arthritis, conjunctivitis, uveitis, episcleritis, erythema nodosum, pyoderma gangrenosum, and hepatic manifestations, such as primary sclerosing cholangitis), and the frequency of flare-ups, with frequent flare-ups defined as >1 flare-up/year,[24] were registered. Disease phenotype (age at onset, duration, location, and behavior, presence of perianal disease) was determined according to the Montreal Classification[25] (non-inflammatory behavior: either stricturing or penetrating disease). Perianal disease and behavior change during follow-up was also registered. Medical therapy was meticulously registered (e.g. steroid, immunomodulator, and biological treatment). AZA intolerance, as defined by the ECCO (European Crohn's and Colitis Organization) Consensus Report,[24] the need for surgery or reoperation (resections in CD), the development of colorectal and small bowel adenocarcinoma, other malignancies, and smoking habits, were investigated by reviewing medical records during follow-up and by questionnaire. Only patients with a confirmed diagnosis for more than one year were enrolled.

The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics and the Csolnoky Ferenc Province Hospital Institutional Committee of Science and Research Ethics.

2.2. Treatment policy

The majority of patients received maintenance therapy with sulfasalazine or a 5-aminosalicylic acid derivative (mesalazine or olsalazine) if tolerated, especially until the mid 1990s. AZA or 6-MP was used as maintenance therapy for steroid dependent, steroid-refractory, or patients with fistulizing disease, in selected cases, mainly after resective surgery before the late-1980s, and on a more frequent basis from the mid-1990s. Short-term oral corticosteroid treatment was used for clinical exacerbations, usually at initial doses of 40–60 mg of prednisone daily, tapered and discontinued over 2–3 months. MTX was only used as a second-line immunomodulator therapy beginning in the mid-1990s. Infliximab has been used for both induction and maintenance therapy in selected cases since the late-1990s. Surgical resections were performed for emergent indications (e.g. obstructive symptoms, hemorrhage), and for failure to respond to medical therapy. Moreover, due to Hungarian health authority regulations, a follow-up visit is obligatory for IBD patients at a specialized gastroenterology center every six months. Otherwise, the conditions of the health insurance policy change and they forfeit their ongoing subsidized therapy. Consequently, the relationship between IBD patients and specialists is a close one.

Definitions of azathioprine/biological use: Patients were regarded as azathioprine users if they took $\geq$1.5 mg/kg for at least 6 months. According to the policy of the centers, AZA, if started, was not stopped, even in patients with long-term clinical remission. Biological therapy was considered to have taken place if the patient received at least a full, anti-TNF induction therapy at an appropriate dose.

2.3. Statistical methods

Variables were tested for normality by Shapiro Wilk's W test. Wilcoxon rank sum test, χ^2-test, and χ^2-test with Yates correction were used to test differences in disease phenotype between subgroups of CD patients for dichotomous variables. Odds ratios (OR) were calculated. The risk for lymphoma and small bowel cancer relative to the general population was estimated using standardized incidence ratios (SIRs, observed/expected) with 95% confidence intervals (CIs) assuming a Poisson distribution for the observed number of cancers. Expected numbers were calculated using the observed age- and sex-specific person-years at risk in the cohort combined with age- and sex-specific intestinal cancer rates from the National Cancer Registry (NCR) and Hungarian Central Statistical Office (KSH). A p-value<0.05 was considered significant. Results for continuous variables are expressed as mean (standard deviation, SD) unless otherwise stated. Peter L. Lakatos performed the statistical analysis. For the statistical analysis, SPSS®15.0 (SPSS Inc, Chicago, IL) was used.

3. Results

3.1. Incidence of lymphoma in patients with inflammatory bowel disease

Of the 1420 patients, we identified three patients who developed lymphoma (one CLL, two low-grade B-cell NHL including one rectal case), in 19,293 patient-years of follow-up (median duration of follow-up: 13 years per patient). All three patients were males. One patient diagnosed with CD at the age of 51 years developed NHL three years later, and at the time of publication is alive, four years after the diagnosis of the lymphoma. In addition, two UC patients developed lymphoma. One patient was 60 years-old at UC diagnosis and 76 years-old at diagnosis of CLL. This first patient died one year later due to causes unrelated to lymphoma. Another patient was 71 years-old at the UC diagnosis and developed NHL at the age of 76. This patient is still alive eight years after the diagnosis of lymphoma. Neither of these patients received AZA or biologicals.

The incidence rate of lymphoma is 1.55 per 10,000 patient-years. Standardized incidence ratio (SIR) was not increased overall with 3 cases observed vs. 2.18 expected (SIR: of 1.37, 95% confidence interval [CI] 0.44–4.26, see Figure 1).

3.2. Association between disease type, phenotype, drug exposure and risk of lymphoma

No significant association was found between disease type, disease phenotype and risk of lymphoma. The SIR was not increased overall in CD with one cases observed vs. 0.71 expected (SIR: 1.41, 95% CI: 0.20–10.1), nor was it increased in UC, with two cases observed vs. 1.47 expected (SIR: 1.35, 95% CI: 0.34–5.42, see Figure 1). However, there was a tendency toward increased incidence in males, with 3 cases observed vs. 1.12 expected (SIR: 2.40, 95% CI: 0.77–7.47, see Figure 2).

Overall, 299 patients were treated with AZA, 11 with anti-TNF agents alone, and 52 with AZA plus an anti-TNF agent. Total AZA exposure was 3649 patient years. The standardized incidence ratio (SIR) was not increased in patients exposed to AZA with no observed cases vs. 0.41 expected.

4. Discussion

The incidence of lymphoma was not increased in this population-based study from Eastern Europe; however there was a tendency toward increased incidence in males. In addition, we were unable to confirm an association with either immunomodulator or biological exposure, although exposure to these drugs (AZA exposure: 3649 patient-years; biological exposure: 40 patient-years) was insufficient to exclude a possible association (Figs. 1 and 2).

Similarly to our findings, IBD itself was not associated with an increased risk of lymphoma in most population-based studies.[11–15] In one of the early reports, Lewis et al.[11] evaluated the risk of lymphoma in nearly 18,000 IBD patients, compared to age-, sex-, and primary care practice-matched controls. Lymphoma rates were also compared with published

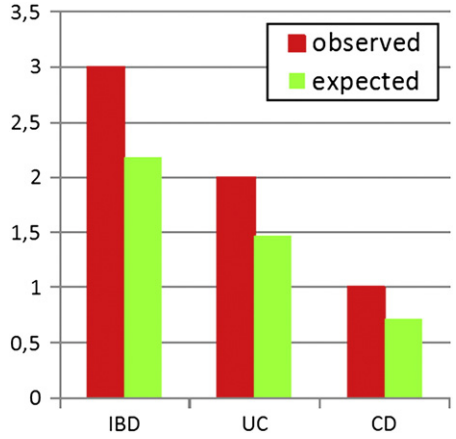

Figure. 1 Overall rate of lymphoma in patients with IBD. SIR_{IBD}: 1.37, 95% CI: 0.44–4.26. SIR_{UC}: 1.35, 95% CI: 0.34–5.42. SIR_{IBD}: 1.41, 95% CI: 0.20–10.1.

age- and sex-specific rates. The incidence of lymphoma was not elevated in CD (RR: 1.39) nor in UC (RR: 1.11), compared to controls. Relative risk of lymphoma among the 1465 IBD patients treated with AZA or 6-MP (average dose: 106 mg/day for 2.0 years) was 1.27. Based on these data, the authors concluded that IBD patients do not have higher risk of lymphoma compared to the general population, but a modestly increased risk of lymphoma with AZA or 6-MP therapy could be not ruled out. Concordantly, in the present study, the SIRs were comparable in CD and UC. In addition, there was no significantly increased risk in UC (SIR: 1.0) and only a borderline-elevated risk in CD (SIR: 1.3, 95% CI: 1–1.7) in a large population-based IBD cohort from Sweden.[15] Furthermore, the authors in the above study failed to identify an association between lymphoma risk and disease extent, calendar period at follow-up, duration of follow-op, inpatient register status, or history of intestinal surgery. In the present study, the low number of lymphoma cases prevented us from performing a meaningful analysis of possible phenotype-lymphoma association. In contrast, similarly to the study by Bernstein et al.[16] (SIR: 3.63; 95% CI: 1.53–8.62) incidence ratios of lymphoma was tendentially increased for males.

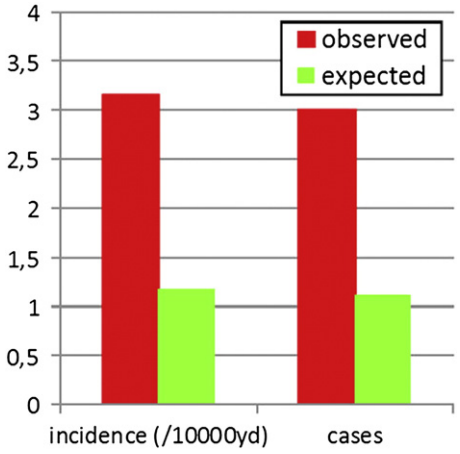

Figure. 2 Overall incidence rate of lymphoma in male patients with IBD. SIR_{male}: 2.40, 95% CI: 0.77–7.47.

A deleterious role of immunomodulators was suggested in the meta-analysis by Kandiel et al.,[17] where the pooled relative risk of lymphoma in CD patients treated with immunomodulators (AZA or MTX) was 4.18 (95% CI: 2.47–7.51). AZA was the concomitant medication in five of the six studies. Sensitivity analysis showed that exclusion of any study had a relatively small effect on the pooled relative risk estimate (range of 3.49–5.21) but excluding either the study with the highest or lowest estimated relative risk eliminated statistically significant heterogeneity. However, a potential limitation is that most studies used retrospective single-center data with low event numbers, as well as relatively short AZA exposure and follow-up. Increased risk of lymphoma was thought to be due to medication, disease severity, or a combination of the two. In addition, the risk of lymphoma was reported to be increased in the CESAME study.[18] At baseline, 30.1% of the patients were receiving an immunomodulator therapy, while 10.0% had discontinued therapy, and 55.5% were immunosuppressant-naïve. One case of Hodgkin disease and 22 cases of NHL were reported. The multivariate-adjusted hazard ratio of lymphoproliferative disorders for patients receiving thiopurines versus those who had never received the drugs was 5.28 (2.01–13.9, p = 0.0007). Of note, however, patients with continuous thiopurine exposure were more likely CD patients with a more severe phenotype (extensive large bowel and perianal disease) as well as more extensive disease in UC patients. Furthermore, follow-up started only after an average of 8.2 years of disease duration. Thus, a potential confounding effect of more severe disease and selection bias could not be fully excluded. In addition, in a very recent report from the Kaiser Permanente IBD registry[26] the risk of lymphoma was only slightly elevated in current AZA users (SIRR: 1.4) and in patient receiving anti-TNF therapy with or without thiopurine (SIRR: 4.4). In contrast, in the present study, none of the lymphoma cases developed in patients with an AZA or biological exposure. A limitation of the present study is however that follow-up under AZA exposure was relatively short, and therefore a modestly increased risk of lymphoma with AZA or 6-MP therapy could not be ruled out. In addition, in a small fraction of the patients (n = 34) the dose of the AZA was below that currently recommended (between 1.5 and 1.75 mg/kg). Another limitation of the present study is the partially retrospective nature of the study that may have led to bias in the interpretation of the data. However, data were collected prospectively since 1985 and the diagnosis of lymphoma can be considered as an unbiased and solid criterion, even retrospectively. In addition, patients with indeterminate colitis were excluded from the study. There were 46 patients with an IC (m/f: 22/24, median age at diagnosis: 36 years) diagnosis. The overall follow-up was 721 patient-years. 11 patients received AZA which corresponds to 143 years drug exposure. None of the patients developed lymphoma.

In the post-transplant setting, most cases of lymphoma are associated with Epstein–Barr virus (EBV) infection.[27] Systemic immunodeficiency caused by the immunosuppression ant combined with local deficiency of EBV-specific immunity may also lead to EBV associated lymphomas.[28] The association is however less clear in non-transplant patients. The importance of infectious pathogens in CD is still debated, EBV is one of the most common pathogen which

can be detected in colonic mucosa of CD patients.[29] Wong, et al., detected EBV in IBD associated lymphomas, but not in IBD associated CRC-s.[30] In addition, Dayharsh et al. identified 18 IBD patients diagnosed with lymphoma at the Mayo Clinic, in Rochester, Minnesota, between 1985 and 2000.[31] Six patients diagnosed with lymphoma were on AZA or 6-MP. Pathology specimens were retrieved and tissue was tested for evidence of EBV by means of *in situ* hybridization. Interestingly, five of the six patients (83%) treated with thiopurine had evidence of EBV in lymphoma tissue, compared to only two of the 10 (20%) patients not on immunomodulator agents (20%). Similar results were reported in a recent nationwide Dutch study where, of the 42 NHL patients, 92% (11/12) of those treated with AZA/6-MP were EBV positive, versus 19% (4/12) in the non-AZA/6-MP-treated group.[32] Somewhat in contrast, in a French study, EBV viral load did not differ significantly between controls and patients with CD, and was not influenced by CD activity or by immunomodulator therapy, including a history of recent IFX infusion.[27] In the present study, none of the patients with lymphoma were exposed to AZA and EBV status was not assessed.

The CESAME group very recently reported that the risk for primary intestinal lymphoproliferative disorders (PILD) was increased in patients with IBD.[19] The reported standardized incidence ratio was 17.5 (95% CI: 6.4–38.1) and the risk was highest in patients exposed to thiopruines (SIR: 49.4; 95% CI: 13.5–126.8). All 14 cases of PILD were non-Hodgkin's B-cell lymphoproliferative disorders; 78.6% occurred in males, 85.7% arose in IBD lesions, and 45.5% were Epstein–Barr virus-positive. Eleven cases occurred in patients with Crohn's disease. Mean (SD) age at PILD diagnosis was 55.1 (5.6) years and the median time since IBD onset was 8.0 years (IQR: 3.0–15.8). In the present study, we observed only a single elderly UC patient with primary rectal lymphoma and data on the prevalence of intestinal lymphoproliferative disorders in non-IBD control population were not available for comparison.

Finally, the risk of lymphoma was reported to be increased in meta-analysis by Siegel et al,[21] in patients receiving anti-TNF agents with previous immunomodulator exposure (SIR: 3.23, 95% CI: 1.5–6.9). Of note, biological exposure was only marginal in the present population-based study; therefore the importance of biological exposure could not be studied.

In conclusion, the overall risk of lymphoma in IBD was not increased in this population-based incident cohort, with only three cases seen over a 30-year period. Similarly, we did not find an association with thiopurine exposure. However, due to the relatively short follow-up under AZA exposure, a definite conclusion on the risk of lymphoma in patients under AZA or 6-MP therapy could be reached.

Conflict of interest statement

No conflicts.

Author contributions

Peter Laszlo Lakatos—study design, data collection, supervising the collection and validation of patients, database construction, statistical analysis, and manuscript preparation; Gyula David, Tunde Pandur, Zsuzsanna Erdelyi, Gabor Mester, Mihaly Balogh, Istvan Szipocs, Csaba Molnar, Erzsebet Komaromi, Agnes Horvath—data collection and manuscript preparation; Barbara Dorottya Lovasz, Petra Anna Golovics, Zsuzsanna Vegh, Michael Mandel, Miklos Szathmari, Lajos S Kiss—database construction and manuscript preparation; Laszlo Lakatos—study design, data collection, supervising the collection and validation of patients, database construction and manuscript preparation; All authors have approved the final draft submitted.

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