Risk of Lymphoma in Patients With Ulcerative Colitis Treated With Thiopurines: A Nationwide Retrospective Cohort Study

NABEEL KHAN,[1,2] ALI M. ABBAS,[1,2,3] GARY R. LICHTENSTEIN,[4] EDWARD V. LOFTUS JR.,[5] and LYDIA A. BAZZANO[1,6]

[1]Section of Gastroenterology, Department of Internal Medicine, Southeast Louisiana Veterans Health Care System, New Orleans, Louisiana; [2]Section of Gastroenterology and Hepatology, Department of Internal Medicine, Tulane University Health Sciences Center, New Orleans, Louisiana; [3]Department of Internal Medicine, University of Florida, Gainesville, Florida; [4]Division of Gastroenterology, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; [5]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; and [6]Department of Epidemiology and Medicine, Tulane University Health Sciences Center for Health Research at Ochsner Health System, New Orleans, Louisiana

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BACKGROUND & AIMS: There is controversy over whether the treatment of patients with ulcerative colitis (UC) with thiopurines increases their risk of lymphoma. We evaluated the risk of lymphoma (ongoing, residual, and per year of therapy) among thiopurine-treated patients with UC. **METHODS:** We obtained nationwide data from the Veterans Affairs (VA) health care system from 2001 to 2011. We performed a retrospective cohort study, analyzing data on 36,891 patients from their date of diagnosis of UC in the VA health care system to a diagnosis of lymphoma or October 1, 2011 (subjects followed up for a median of 6.7 years). Thiopurine exposure was assessed using the VA pharmacy database. Patients who developed lymphoma were identified based on ICD-9 codes and confirmed by manual chart review. **RESULTS:** In total, 4734 patients with UC (13%) were treated with thiopurines for a median of 1 year. Lymphoma developed in 119 patients who had not been treated with thiopurines, 18 who were treated with thiopurines, and 5 who had discontinued treatment with thiopurines. The incidence rates of lymphoma were 0.60 per 1000 person-years among patients who had not been treated with thiopurines, 2.31 among patients who were treated with thiopurines, and 0.28 among patients who had discontinued treatment with thiopurines. The incidence rates of lymphoma during the first year, second year, third year, fourth year, and >4 years of thiopurine therapy were 0.9, 1.6, 1.6, 5, and 8.9 per 1000 person-years, respectively. The age-, sex-, and race-adjusted hazard ratios of developing lymphoma were 4.2 (95% confidence interval, 2.5–6.8; $P < .0001$) while being treated with thiopurines and 0.5 (95% confidence interval, 0.2–1.3; $P = .17$) after discontinuing treatment with thiopurines compared with patients who had not been treated with thiopurines. **CONCLUSIONS: Based on a retrospective, nationwide cohort study, patients with UC have a 4-fold increase in risk of lymphoma while being treated with thiopurines compared with patients who have not been treated with thiopurines. The risk increases gradually for successive years of therapy. Discontinuing thiopurine therapy reduces the risk of lymphoma.**

Keywords: IBD; Inflammatory Bowel Disease; Cancer Risk; Medication.

Ulcerative colitis (UC) is a chronic inflammatory disorder of unknown etiology. Based on the largest study of prevalence to date, we estimate that more than 700,000 Americans are currently living with UC.[1] Corticosteroids are commonlvy used for induction of remission in patients with UC.[2] However, they are associated with a number of adverse effects, including weight gain, mood disorders, and osteoporosis, and often lack long-term efficacy.[3–6] These 2 issues have encouraged a number of corticosteroid-sparing therapies to be used in patients with UC. Such therapies include thiopurines (azathioprine and 6-mercaptopurine) and anti–tumor necrosis factor agents such as infliximab and adalimumab. Although these medications spare patients from the potential adverse effects of long-term use of corticosteroids, they have their own spectrum of side effects. Lymphoma is one of the most concerning and potentially lethal adverse outcomes of immunosuppressive therapy and has been linked to treatment with thiopurines.[7]

Immunosuppressive therapies may contribute to the development of lymphoma in a variety of ways. Decreased immune surveillance of Epstein–Barr virus (EBV)-infected B cells is believed to contribute to development of lymphoma,[8] and use of thiopurines in particular has been implicated in the development of EBV-positive lymphomas.[9–13] Moreover, thiopurines may cause direct damage to DNA by incorporating thiopurine nucleotides during replication, which renders DNA unstable and interferes with further replication cycles and repair mechanisms, resulting in mutations.[14–17]

Use of thiopurines is widely accepted as a risk factor for lymphoproliferative disorders, including lymphoma, in post–organ transplant settings. Some reports suggest that they increase the risk of lymphoproliferative diseases by up

Abbreviations used in this paper: 5-ASA, 5-aminosalicylic acid; CI, confidence interval; EBV, Epstein–Barr virus; HR, hazard ratio; IBD, inflammatory bowel disease; ICD-9, International Classification of Diseases, Ninth Revision; IQR, interquartile range; SEER, Surveillance Epidemiology and End Results; UC, ulcerative colitis; VA, Veterans Affairs.

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to 20- and 200-fold for renal and heart transplant recipients, respectively.[7] However, there is no such consensus about the extent of this risk for patients with inflammatory bowel disease (IBD) who are treated with thiopurines. Some studies have reported no increase in risk,[18,19] whereas another study reported an increase of 31 times.[20] To date, 4 population-based cohorts have addressed this issue in the United States and Europe, and they showed conflicting results.[21–24] Similarly, the 2 published meta-analyses failed to reach a consesnsus.[25,26]

The Veterans Affairs (VA) administration has the largest integrated health care system in the United States, serving approximately 8.3 million veterans each year.[27] We used the VA population-based database to (1) estimate the risk of lymphoma among patients who were treated with thiopurines compared with patients with UC who were not treated with this class of medication, (2) investigate the potential residual risk of lymphoma after discontinuation of treatment with thiopurines, and (3) evaluate the effect of the cumulative duration of thiopurine therapy on the incidence rate of lymphoma.

Patients and Methods

Study Population

Nationwide data were obtained from the VA Pharmacy Benefits Management and Corporate Data Warehouse databases. Veterans who were seen and followed up in the VA health care system from October 1, 2001, to October 1, 2011, were identified using the International Classification of Diseases, Ninth Revision (ICD-9) codes for UC (556.xx). The study was approved by the institutional review board of the Southeast Louisiana Veterans Health Care System.

Study Design

We conducted a retrospective cohort study in which patients with UC were followed up from the index date (first ICD-9 code for UC entered in their record in the VA system during the observation period) or the first time they filled a prescription for 5-aminosalicylic acid (5-ASA) compounds from the VA pharmacy if that preceded the entry of the first ICD-9 code (start date). Follow-up was concluded at the time the patients developed lymphoma (our outcome of interest) or October 1, 2011 (end of the observation period). To be included in the analysis, the patients had to have been followed up in the VA system for at least 1 month (ie, a minimum follow-up duration between the start and the end day of 1 month).

Assessment of Lymphoma Outcome

The medical records of the identified patients with UC were queried for the presence of a diagnosis of lymphoma using ICD-9 codes (200–202.28, 202.7–202.98). The medical charts of the identified cases were manually reviewed to confirm the diagnosis of lymphoma according to preset criteria that consider biopsy results or a note from a hematologist as adequate for correct diagnosis. The date, type, and location of lymphoma were abstracted from the charts. We excluded prevalent cases of lymphoma (ie, patients diagnosed with lymphoma before October 1, 2001, or a diagnosis of UC). To identify the current and residual effects that thiopurine therapy might have on the risk of lymphoma, we classified the identified cases as those occurring during or up to 6 months after thiopurines therapy (coincidental) as compared with lymphoma diagnosed after discontinuation of thiopurine therapy for 6 months or more (noncoincidental).

Assessment of Exposure and Other Predictors

Automated data abstraction from the VA pharmacy database was used to identify periods of exposure to thiopurines during the follow-up period. Person-years of exposure to thiopurines were calculated in a time-dependent manner, accounting for the initiation and discontinuation of therapy, with a study subject potentially contributing person-years of follow-up to any or all the 3 exposure categories: (1) unexposed, follow-up periods from all the patients who never filled a prescription for a thiopurine and the period before the first filling for those who were treated with thiopurines; (2) during exposure, periods of exposure to thiopurines started at the filling day and ended when the medication day supply was exhausted; (3) after stopping, follow-up periods after the last prescription for a thiopurine was exhausted and the gaps between exposure periods if present.[21,23] Data on other predictors, such as age at the start of follow-up (younger than 40, 40–64, older than 65 years of age), sex, and race, were also collected.

Exposure to infliximab during the follow-up period was identified as present versus absent due to its low prevalence in the VA system (1%). We calculated the incidence rates of lymphoma among those treated with infliximab as monotherapy or in combination with thiopurines, and we performed a sensitivity analysis after excluding those treated with infliximab to identify its effect on the observed lymphomas.

Statistical Analysis

To study the effect of ongoing and past thiopurine therapy on the risk of lymphoma, all patients with UC were included, and the incidence rate of lymphoma (per 1000 person-years) was calculated for unexposed patients, those currently being treated with thiopurines, and those who discontinued thiopurine therapy. Exposure to thiopurines was included in a multivariate Cox regression model as a time-dependent variable. The age-, sex-, and race-adjusted hazard ratios (HRs) of lymphoma for patients while on thiopurine therapy and after discontinuing therapy as compared with unexposed patients were calculated.

To improve the generalizability of our findings, the aforementioned incidence rates were adjusted for age using weights that represent the age group proportions of the 2000 US standard population. Standardized incidence ratios of non-Hodgkin lymphoma were calculated by comparing these rates with the age-adjusted rate of non-Hodgkin lymphoma as reported by the Surveillance Epidemiology and End Results (SEER) database.[28]

We investigated the effect of the cumulative duration of thiopurine therapy on the incidence of lymphoma by performing a life table analysis with the follow-up time classified into 5 intervals at the end of each year (first year, second year, third year, fourth year, and beyond 4 years) of exposure or follow-up (Table 4). For each interval, we identified the total population at the start of the interval, person-year contribution, and number of lymphoma cases that were diagnosed during the interval. The latter 2 parameters were used to calculate the per-year incidence rate of lymphoma for those who were treated with thiopurines and those who were not. We then compared the rate of lymphoma occurrence between the exposed and unexposed participants within each interval using a multivariate Cox regression analysis adjusted for age, sex, and race.