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Observations and Research

Risk of Primary Gastrointestinal Lymphoma in Patients With Inflammatory Conditions Exposed to Tumor Necrosis Factor Alpha Inhibitors and Immunomodulators: A Case–Control Study

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Introduction: The aim of this case–control study was to determine if exposure to tumor necrosis factor alpha inhibitors (TNFIs) or immunomodulators (thiopurines or methotrexate) was associated with development of primary gastrointestinal lymphoma (PGIL) in patients with chronic inflammatory conditions.

Methods: Patients with PGIL and controls evaluated at a tertiary care center over 20 years were matched 1:3 using a medical record informatics search engine based on their chronic inflammatory condition (Crohn's disease [CD], ulcerative colitis [UC], rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis) and duration of follow-up. Patients who started on TNFI within 3 months of PGIL diagnosis were excluded. We extracted demographics, medical history, and medications used. Univariate models using conditional logistic regression were used due to the small number of matched pairs.

Results: Twenty PGIL cases matched with 60 controls were followed for a mean 9.9 ± 6.9 and 9.7 ± 8.6 years, respectively. Mean age at time of PGIL diagnosis was 47.5 ± 22.0 (standard deviation) years and the majority (75%) were males. The most common inflammatory diagnosis was inflammatory bowel disease (80% of cases; 45% with UC and 35% with CD). Development of PGIL was not associated with TNFI (odds ratio [OR] = 2.6; 95% confidence interval [CI] 0.69–11.01; $P = .18$), but with use of TNFI in combination with thiopurines (OR = 8.93; 95% CI 1.43–80.25; $P = .014$). Risk of PGIL increased with every additional TNFI (2.277 (1.002–5.713); $P = .0494$). All cases exposed to multiple TNFI were also exposed to thiopurines. Use of thiopurines (alone or in combination) was the greatest risk factor (OR = 6.32; 95% CI 1.55–37.05; $P = 0.006$) to develop PGIL.

Conclusions: TNFI therapy was not associated with increased risk for PGIL unless used in combination with thiopurines and with every switch to a different TNFI.

Lay Summary

Tumor necrosis factor alpha inhibitors (TNFs) treat inflammatory bowel disease and other inflammatory conditions. This study found that TNFIs were not associated with increased risk primary gastrointestinal lymphoma, unless combined with thiopurines and with every switch to a different TNFI.

Key Words: Crohn's disease, ulcerative colitis, psoriatic arthritis, rheumatoid arthritis, thiopurines

Introduction

Tumor necrosis factor alpha inhibitors (TNFIs) were initially approved by the Food and Drug Administration (FDA) in 1998 for moderate-to-severe Crohn's disease (CD; infliximab) and rheumatoid arthritis (RA; etanercept).[1,2] They are now used in several chronic inflammatory conditions including CD, ulcerative colitis (UC), ankylosing spondylitis (AS), and psoriatic arthritis (PsA). The use of TNFI has been associated with the development of non-Hodgkin lymphoma and hepatosplenic T-cell lymphoma, particularly when used in combination with thiopurines.[3–5] However, a possible association between TNFI monotherapy and primary gastrointestinal lymphoma (PGIL) has not been studied.

PGIL is a rare type of lymphoma, accounting for 1%–4% of gastrointestinal malignancies.[6] Chronic inflammation, such as in RA, and immunosuppression are known risk

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factors for the development of lymphoma.[7–9] In patients with inflammatory bowel disease (IBD), exposure to thiopurines has been consistently associated with an increased incidence of lymphoma,[10–13] while exposure to TNFI as a risk factor is still controversial and the risk has been mostly attributed to concomitant use of thiopurines.[14] Similarly, the incidence of PGIL has been shown to be increased in patients with IBD exposed to thiopurines.[13]To date, the risk of PGIL with TNFI exposure could not be adequately assessed due to small numbers of cases. A recent multicenter European case series, including 15 IBD patients with PGIL, showed that most cases occurred in male patients (80%) with prior exposure to thiopurines (46%).[15] It remains unclear if exposure to TNFI monotherapy is associated with increased risk of developing PGIL.

Our aim was to perform a case–control study to determine if exposure to TNFI or immunomodulators (thiopurines or methotrexate) was associated with the development of PGIL in patients with chronic inflammatory conditions (UC, CD, RA, PsA).

Methods

Cases

Cases were identified using an electronic medical record informatic search engine and defined as patients with a chronic inflammatory disorder (CD, UC, RA, AS, PsA) that were diagnosed with a PGIL (based on pathology report confirmation between 2/1999 and 2/2019). Patients who were on TNFI within 3 months of GI lymphoma diagnosis and those who did not consent to participate in research studies were excluded. Patients with mucosa-associated lymphoid tissue lymphoma and those with enteropathy-associated T-cell lymphoma (EATL) were excluded due to their unique associations with *Helicobacter pylori* infection and celiac disease, respectively. The study was approved by Mayo Clinic Institutional Review Board (IRB #19-003213).

Controls

Cases were matched 1:3 with non-lymphoma cases for the exact underlying inflammatory disorder (CD, UC, RA, AS, PsA), and within an age of ±10 years at the time of diagnosis of inflammatory disease. Controls had to have been followed without a lymphoma diagnosis for at least as long as the case was followed from the time of inflammatory condition diagnosis until the time of lymphoma diagnosis. Patient electronic medical records were examined to extract demographic information, medical history, and medications used.

Statistical Analysis

Descriptive statistics are reported as number (percentage) for discrete variables and as mean (standard deviation [SD]) for continuous variables. Univariate models were examined for variable associations with gastrointestinal lymphoma case status using exact conditional logistic regression to account for the 3:1 matched status of patients. Exact was used due to the small number of matched pairs (20 matches). The alpha level was set at 0.05 for statistical significance. All analyses were completed using SAS version 9.4.

Results

Demographics and Clinical Characteristics

A total of 20 cases of PGIL on a background of inflammatory condition were identified and matched to 60 controls with corresponding inflammatory conditions and no PGIL (Table 1). In the PGIL case group, the mean age at time of the inflammatory condition diagnosis was 39.5 ± 21.9 (SD) years and the majority were males (75%) with either a current (2/20) or former (6/20) history of smoking. The mean duration from the time of the inflammatory condition diagnosis was 14.3 ± 6.3 years. The mean age at the time of PGIL diagnosis was 47.5 ± 22.0 years. The mean follow-up at Mayo Clinic was 9.9 ± 6.9 years.

In the control group without PGIL, the mean age was 33 ± 18.3 years and there was equal sex distribution (50% males, 50% females). Current and former smoking were documented in 8 (13.3%) and 13 (21.7%), respectively. The mean duration with the inflammatory diagnosis was 16 ± 11.5 years. The mean follow-up at Mayo Clinic was 9.7 ± 8.6 years.

The most common inflammatory conditions in both PGIL cases and controls were UC (45% and 36.7%, respectively) and CD (35% and 36.7%, respectively).

Among cases, the most common locations of PGIL were in the colon (45%) and small bowel (45%). In the colon, 30% were in the ascending, transverse, descending, or sigmoid colon, 10% in the rectum, and 5% in the cecum. In the small bowel, the most common location was the ileum (20%) followed by the jejunum (15%), and the least common location was the duodenum (10%). The most common types of PGIL were diffuse large B-cell lymphoma (DLBCL, 35%) followed by follicular B-cell lymphoma (20%). Around half of cases had positive Epstein Barr virus serology (45%).

Medication Exposure

Current use of TNFI was found in 30% (6/20) of PGIL cases and 25% (15/60) of controls, while previous exposure to TNFI was found in 25% (5/20) of PGIL cases and 11.7% (7/60) of controls (Table 2). The mean duration in years of TNFI exposure was similar between PGIL cases and controls (3.5 years compared to 5.1 years). Most cases and controls were treated with a single TNFI (25% PGIL cases vs. 21.7% of controls), while in 25% of PGIL cases, there had been a switch to a second TNFI compared to 15% of controls. Only 1/20 (5%) of the cases required switch to a third TNFI compared to none of the controls. The most common first TNFI used in both groups was infliximab (50% in cases and 20% in controls), while the most common second TNFI used was adalimumab (25% in cases and 10% in controls). The mean time from the initiation of TNFI to the PGIL diagnosis was 5.5 ± 4.5 years in the cases.

Current thiopurine use was found in 15% of controls. As expected, given the diagnosis of lymphoma, no patients in the case group had current use of thiopurines. The majority (65%) of PGIL case group were exposed to thiopurines in their inflammatory condition disease course, compared to only 30% in the control group. Combination therapy with concomitant use of thiopurines and a TNFI was found in 45% of PGIL cases and 21.7% of controls. Thiopurines were used as single agents in 20% of PGIL cases and 8.3% of controls. Methotrexate use was found in 20% of cases and

Table 1. Characteristics of patients with primary gastrointestinal (GI) lymphoma (cases) and controls.

	Cases *N* = 20	Controls *N* = 60
Mean age at time of inflammatory diagnosis, years (SD)	39.5 (21.9)	33.0 (18.3)
Mean age at time of lymphoma diagnosis, years (SD)	47.5 (22.0)	-
Sex, male, *N* (%)	15 (75)	30 (50)
Mean time with inflammatory diagnosis, years (SD)	14.3 (6.3)	16.0 (11.5)
Mean follow-up, years (SD)	9.9 (6.9)	9.7 (8.6)
Smoking status, *N* (%)		
Current	2 (10)	8 (13.3)
Former	6 (30)	13 (21.7)
Inflammatory condition, *N* (%)		
Ulcerative colitis	9 (45)	22 (36.7)
Crohn's disease	7 (35)	22 (36.7)
Psoriasis	3 (15)	10 (16.7)
Rheumatoid arthritis	1 (5)	6 (10.0)
Type of gastrointestinal lymphoma, *N* (%)		-
Diffuse large B-cell lymphoma	7 (35)	-
Follicular B-cell lymphoma	4 (20)	-
Hodgkin's lymphoma	3 (15)	-
Mantle cell	2 (10)	-
T-cell lymphoma	2 (10)	-
Plasmablastic B-cell lymphoma	1 (5)	-
T-cell anaplastic large cell	1 (5)	-
Location of gastrointestinal lymphoma, *N* (%)		-
Colon	6 (30)	-
Cecum	1 (5)	-
Rectum	2 (10)	-
Ileocolonic (ileum and right colon)	1 (5)	-
Ileum	4 (20)	-
Duodenum	2 (10)	-
Jejunum	3 (15)	-
Stomach	1 (5)	-
EBV status based on serology, *N* (%)		
Positive	9 (45)	-
Negative	5 (25)	-
Unknown	6 (30)	-

Abbreviations: 5-ASA, aminosalicylic acid; EBV, Epstein Barr virus; *N*, number; SD, standard deviation; TNFI, tumor necrosis factor alpha inhibitors.

11.7% of controls. Information on other medications used including aminosalicylic acids (5-ASA) and corticosteroids are documented in Table 2.

Risk Factors for PGIL

Exposure to TNFI in general was not significantly associated with PGIL (OR = 2.636 (0.699–11.014); $P = .178$), as shown in Table 3. The exposure to thiopurines, whether alone or in combination with TNFI, showed a significantly increased risk of PGIL (OR = 6.320 [1.553–37.055]; $P = .006$), while use of methotrexate was not associated with developing PGIL (OR = 2.000 [0.350–11.348]; $P = .548$). Combination therapy (TNFI with thiopurines) was associated with a significantly increased risk of developing PGIL (OR = 8.93 [1.43–80.25]; $P = .014$). Patients treated with thiopurines as a single agent had increased risk of PGIL (OR = 5.395 [0.804–44.341]; $P = 0.089$). In individuals who were exposed to TNFI as a single agent only, the associated risk with PGIL was not significantly increased (OR = 1.744 [0.129–17.535]; $P = .900$). Only 1 patient in the study was exposed to a non-TNFI (1 patient in the case group had been exposed to vedolizumab), limiting interpretation of statistical analysis. Exposure to corticosteroids did not increase the risk of PGIL (OR = 0.702 [0.188–2.732]; $P = .748$). Similarly, exposure to 5-ASA was not associated with increased risk of PGIL (OR = 0.886 [0.177–4.476]; $P = 1.0$). Furthermore, with every additional switch to a new TNFI, there was an associated significant increase in risk of PGIL (2.277 [1.002–5.713]; $P = .0494$) (Table 3). Exposure to more than 1 TNFI occurred in 30% of cases and 15% of controls. All of the cases (6/6) and 77.8% (7/9) of controls exposed to more than 1 TNFI were exposed to thiopurines as well.

Table 2. TNFI and other medication exposures in cases and controls.

	Cases (*N* = 20)	Controls (*N* = 60)
TNFI exposure, *N* (%)		
Never	9 (45)	38 (63.3)
Current	6 (30)	15 (25)
Past	5 (25)	7 (11.7)
Mean duration of TNFI exposure, years (SD)	3.5 (4.2)	5.1 (4.6)
Mean time from TNFI to diagnosis of lymphoma, years (SD)	5.5 (4.5)	-
Number of TNFI exposure, *N* (%)		
One	5 (25)	13 (21.7)
Two	5 (25)	9 (15)
Three	1 (5)	0 (0)
First TNFI, *N* (%)		
Infliximab	10 (50)	12 (20)
Adalimumab	0 (0)	7 (11.7)
Etanercept	1 (5)	1 (1.7)
Certolizumab	0 (0)	2 (3.3)
Second TNFI, *N* (%)		
Infliximab	0 (0.)	1 (1.7)
Adalimumab	5 (25)	6 (10.0)
Etanercept	0 (0)	1 (1.7)
Certolizumab	1 (5)	1 (1.7)
Third TNFI, *N* (%)		
Infliximab	1 (5)	0 (0)
Immunomodulator exposure		
Thiopurine exposure, *N* (%)		
None	7 (35)	42 (70)
Current	0 (0)	9 (15)
Past (use for >5 years)	1 (5)	4 (6.7)
Past (used for 2–5 years)	1 (5)	3 (5.0)
Past (used for <2 years)	11 (55)	2 (3.3)
Methotrexate exposure, *N* (%)	4 (20)	7 (11.7)
Past 5-ASA exposure, *N* (%)	11 (55)	34 (56.7)
Corticosteroid exposure, *N* (%)		
Current	5 (25)	7 (11.7)
Past use	8 (40)	36 (60)
Other medications, *N* (%)		
Tacrolimus	1 (5)	1 (1.7)
Hydroxychloroquine	1 (5)	2 (3.3)
Vedolizumab	1 (5)	0 (0)
6-Mercaptopurine	0 (0)	3 (5)
Therapy options, *N* (%)		
Combination therapy (TNFI + thiopurine)	9 (45)	13 (21.7)
TNFI single agent	2 (10)	9 (15)
Thiopurine single agent	4 (20)	5 (8.3)
Neither TNFI nor thiopurine	5 (25)	33 (55)

Abbreviations: *N*, number; SD, standard deviation; TNFI, tumor necrosis factor alpha inhibitors.

Discussion

In this case–control study, we evaluated whether exposure to TNFI or immunomodulators (thiopurines or methotrexate) was a risk factor for the development of PGIL in patients with chronic inflammatory conditions. A total of 20 cases of PGIL were identified and the majority had IBD (80%). We found that exposure to TNFI was not a risk factor (OR = 2.6; $P = .178$) unless used in combination with thiopurines (OR = 8.9; $P = .014$). Exposure to thiopurines alone or in combination with TNFI was associated with the development of PGIL (OR 6.3; $P = .006$), while methotrexate was not a risk factor for PGIL.

Table 3. Risk factors for development of lymphoma, univariate analysis with logistic regression.

	Odds ratio (95% CI)	*P*-value
Individual risk of each medication exposure		
TNFI use	2.636 (0.699–11.014)	.178
Per each additional TNFI used	2.277 (1.002–5.713)	.0494
Thiopurine use	6.320 (1.553–37.055)	.006
Methotrexate use	2.000 (0.350–11.348)	.548
Corticosteroid use	0.702 (0.188–2.732)	.748
5-ASA use	0.886 (0.177–4.476)	1.0
Therapy[a]		
Combination	8.930 (1.435–80.252)	.014
Thiopurine single agent	5.395 (0.804–44.341)	.089
TNFI single agent	1.744 (0.129–17.535)	.900
Neither thiopurine nor TNFI	1.0 (reference)	

Abbreviations: 5-ASA, aminosalicylic acid; CI, confidence interval; TNFI, tumor necrosis factor alpha inhibitors.
[a]The overall association of the 4-level association is $P = .051$.

To date, 4 case series on PGIL in IBD patients have been reported,[13,16] including a recent multicenter European case series.[15] Combined, those studies have reported a total of 47 patients. The majority were males (85%) with history of immunosuppression use, particularly thiopurines (38% of cases). Exposure to TNFI was only reported in 3 cases (2 from the most recent European case series). The previous Mayo Clinic series from Holubar et al.[16] only included patients from the pre-biologic era (prior to the FDA approval of TNFI in 1998), while the French national cohort CEMUSE by Sokol et al.[13] included PGIL cases between 2004 and 2005. In agreement with the prior literature, most PGIL cases described in this study occurred in middle-aged males (75%), with median age of 47 years at the time of diagnosis of PGIL diagnosis, and history of thiopurine exposure. In the current case–control study, TNFI use was reported in 55% of cases ($n = 11/20$) compared to 36.7% ($n = 22/60$) in controls. The most common underlying chronic inflammatory condition among PGIL cases in this study was IBD ($n = 16$), specifically UC ($n = 9$). This is in contrast with other studies that reported CD as the most common underlying IBD diagnosis in cases that developed PGIL.[13]

Thiopurine use has been consistently associated with the development of lymphoma in patients with IBD, particularly in males.[5,17] This risk appears to be greatest after 2 years of exposure.[5,17] Although most cases of lymphoma are B-cell lymphomas, young males exposed to thiopurines are at particularly high risk of development of hepatosplenic T-cell lymphoma, which carries a poor prognosis.[18] On the other hand, while some studies have suggested that TNFI may increase the risk of lymphoma,[5] most studies have not found a clear association unless used in combination with thiopurines.[14,19] Of note, while combination concomitant use of TNFI and thiopurines is commonly used in the IBD population, it is not routinely used for rheumatological conditions. In this study, thiopurine exposure was associated with an increased risk of PGIL (odds ratio [OR] 6.3; $P = .006$). Interestingly, combination therapy with TNFI and thiopurines conferred the greatest risk (OR = 8.9; 95% confidence interval [CI] 1.435–80.252; $P = .014$), which could suggest a synergistic effect leading to development of PGIL. Similarly, others have reported combination therapy as the highest risk factor overall for development of PGIL.[5] Therefore, although TNFI use alone was not significantly associated with increased risk of PGIL (OR = 2.636; 95% CI 0.699–11.014; $P = .178$), these data should be interpreted with caution. Furthermore, future switching to new TNFI increased the risk of PGIL in individuals already exposed to thiopurine.

Limitations of this study include its retrospective design and relatively small number of cases which precludes multivariate analysis. Another limitation includes the tertiary care referral nature of the Mayo Clinic practice, but this was mitigated by including patients with considerable duration of follow-up at Mayo Clinic. There was some heterogeneity between the case and control groups regarding age of inflammatory diagnosis and sex (majority of cases were males). Another limitation, resulting from the retrospective design of the study, was the difficulty in determining the exact start and end date of certain medications, particularly thiopurines, but we relied on a thorough medical record review and obtained information from the documented notes of the providers. Data regarding disease severity were not available and therefore contribution of chronic inflammation as a risk factor cannot be ruled out. This is the first case–control study, to our knowledge, to assess the association between the exposure to TNFI and immunomodulators and the risk of PGIL in patients with chronic inflammatory conditions.

In summary, exposure to TNFI alone was not associated with an increased risk of PGIL in patients with chronic inflammatory conditions compared to controls. However, thiopurine exposure increased the risk of PGIL, which is consistent with prior studies linking thiopurines with lymphoma in general. Long-term use of thiopurine in patients with chronic inflammatory diseases should be approached with caution.

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Author Contributions

M.B.N.: Manuscript draft, data collection. J.N.: Data collection. S.H.: Statistical analysis. I.W.: Important intellectual content. L.R.: Important intellectual content. V.C.: Study design, data interpretation, senior author. M.C.: Study design, data interpretation, senior author.

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Conflicts of Interest

The authors have no relevant conflicts of interest.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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