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Outcome of inflammatory bowel disease patients with prior malignancy

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Abstract

Background Inflammatory bowel disease (IBD) treatment options, such as anti-tumor necrosis factor (TNF) agents and thiopurines, are associated with an increased risk of certain malignancies. However, the management of IBD patients with prior malignancy is not well defined and the literature is scarce. The main aim of this study was to describe the outcome of IBD patients with prior malignancy, or malignancy before first exposure to IBD-related biologic or immunosuppressive treatment.

Methods The study cohort included adult IBD patients followed in a tertiary academic center, with at least one malignancy diagnosed before IBD diagnosis or before initiation of IBD-related treatment. The main outcome of interest was a relapse of the previous malignancy or development of a second malignancy.

Results Our database included 1112 patients with both IBD and malignancy. Of these, 86 (9%) who had their malignancy diagnosed before IBD-related treatment initiation were identified, while 10/86 patients (9%) were further diagnosed with a second primary malignancy. Twenty patients, (20/86, 23%) had recurrence of a previous malignancy, most commonly non-melanoma skin cancer (NMSC), found in 9/20 patients (45%). Treatment with infliximab was found to be significantly associated with recurrence of NMSC (P=0.003).

Conclusions Anti-TNF treatment may be associated with an increased risk of NMSC recurrence. This underscores the importance of rigorous dermatological follow up in IBD patients with previous NMSC treated with anti-TNFs.

Keywords Inflammatory bowel disease, therapy, malignancy, recurrent, secondary

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Introduction

Patients with inflammatory bowel disease (IBD) have an increased overall risk of malignancy [1]. Although rising life expectancy may contribute to the prevalence of diagnosed IBD patients presenting with malignancies, there is concern over an association between certain IBD-related treatments and malignancy.

It is necessary to differentiate between primary, secondary and recurrent malignancy. Thiopurines are known to increase the risk for primary lymphoma and non-melanoma skin cancer (NMSC) in the context of IBD treatment [2,3]. The evidence for an association with biological treatments, specifically anti-tumor necrosis factor (TNF) agents, is more controversial. Some studies found a positive association between anti-TNFs and the risk for lymphoproliferative disorders [4], while other large studies challenged this finding [5].

In contrast to primary malignancy, the literature on secondary or recurrent malignancy among patients with IBD is more equivocal; a large trial from the Cancers Et Surrisque Associé aux Maladies inflammatoires intestinales En France (CESAME) group concluded that immunosuppressive therapy has no impact on the risk of recurrence, although this conclusion

cannot be applied for anti-TNF therapies [6]. Additionally, a large recent study from Denmark, which included patients with IBD, rheumatoid arthritis (RA) or psoriasis and prior cancer, demonstrated that the use of anti-TNFs was not associated with recurrent malignancy [7]. Furthermore, a large network meta-analysis that checked all immune-mediated diseases, including IBD, found no increased risk for recurrent cancers with conventional immunosuppressants or anti-TNFs [8]. The latest European Crohn's and Colitis Organisation consensus guidelines conclude that the available data from studies of patients with IBD or other immune-mediated inflammatory conditions (such as RA) exposed to anti-TNFs demonstrate no obvious excess risk for new or recurrent cancer. However, general caution and a multidisciplinary evaluation were suggested for the selection of appropriate treatment on a case-by-case basis [9].

While the association is not definitive, physicians should still consider the risk of active IBD treatment against immunosuppressive sequelae for every patient. The main objective of this study was to investigate whether IBD patients with prior malignancy and IBD-specific treatment after the diagnosis of the first malignancy have a higher risk for a second malignancy.

Patients and methods

Study design

This was a retrospective, observational cohort study.

Population

We scanned the IBD patient database for diagnoses of current or prior malignancy among adult patients who were being routinely followed-up at the department of gastroenterology in Sheba Medical Center, Israel, between January 2010 and December 2021.

Patients were included if they met the following criteria: (1) confirmed diagnosis of ulcerative colitis or Crohn's disease; (2) confirmed diagnosis of prior or current malignancy; and (3) IBD diagnosed after cancer, or cancer was already known at the point IBD treatment was initiated.

IBD treatments were defined as past or current exposure to at least one of the following medications: thiopurines, TNF-α blockers, methotrexate, tofacitinib, vedolizumab and ustekinumab. Treatment with 5-aminosalicylates or corticosteroids was not addressed in our analysis.

Data collection

The following data was extracted from electronic medical records: age at IBD and malignancy diagnosis, IBD subtype, date of cancer diagnosis, type of cancer, and IBD treatment exposure after a cancer diagnosis. Cancer types were categorized into gastrointestinal, hematologic (leukemia or lymphoma), dermatologic (melanoma and NMSC), or other solid organs.

Outcomes

The main outcome of this study was identifying a relapse of a previously diagnosed malignancy or the development of a secondary malignancy. We assessed the association of different IBD treatments with the risk for relapse or secondary malignancy. Previous malignancy was defined in those with electronical documentation of active disease before this study period. Malignancy relapse was defined as documented evidence for recurrence after confirmed recovery. A new malignancy in patients with previous malignancy was defined as any subsequent incidence of a new primary tumor.

Statistical analysis

Descriptive statistics for demographic and clinical characteristics included median (interquartile range [IQR]) for continuous variables and frequency distributions for categorical data. Simple logistic regression was used to calculate odds ratios for the risk of second malignancy or first malignancy relapse. A 2-sided P-value of <0.05 was determined to be statistically significant. Kaplan-Meier survival analysis was applied to plot cumulative events. Statistical analysis was performed using the Software Package for Statistics and Simulation (IBM SPSS version 25, IBM, Corp, Armonk, NY).

Ethical considerations

The study was approved by the institutional review board.

Results

Patients

Out of 8366 IBD patients in the database, we identified 1112 adult patients with IBD and malignancy. To maximize data validity, patients who were followed-up (for their IBD or malignancy) at other institutions were excluded. The final study population included a total of 86 patients whose IBD was diagnosed after cancer or cancer was already known at the point of IBD treatment initiation (Fig. 1). All patients have been followed up solely and consistently in our institution.

The final cohort was divided into 2 subgroups. The first subgroup (Group A*)* included 38/86 patients (44%) who were diagnosed with malignancy before IBD. The second subgroup (Group B) included 48/86 patients (56%) who were diagnosed with malignancy after IBD, but before their first exposure to IBD-related treatment. Patients' characteristics are detailed in Table 1.

In Group A, 20/38 patients (53%) were male, and 28/38 patients (74%) were current smokers. The median age of malignancy diagnosis was 45 (IQR 39-53), and the median time lapse between malignancy and IBD diagnosis was 6 years (IQR 3-12).

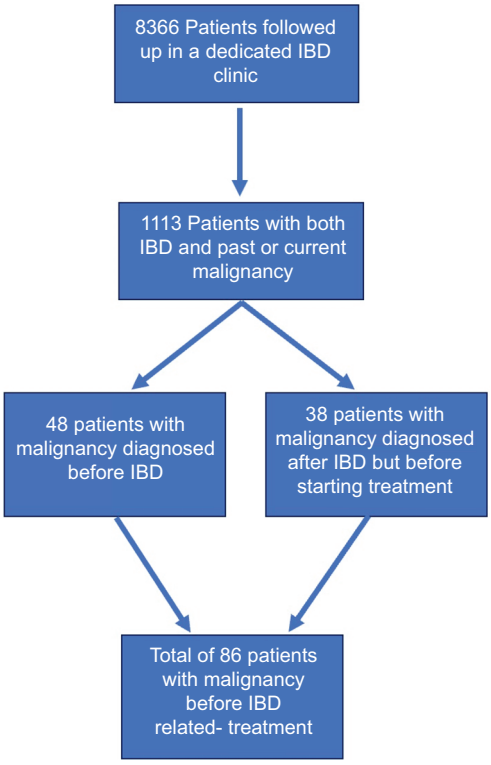

Figure 1 Cohort data workflow
IBD, inflammatory bowel disease

In Group B, 26/48 (57%) patients were male and 19/46 (40%) were current smokers. The median age when malignancy was diagnosed was 53 years (IQR 47-59), and the median time lapse between IBD and malignancy was 15 years (IQR 7-22).

First malignancies

The most prevalent malignancy in group A (i.e., before diagnosis of IBD) was breast cancer, found in 9/38 (24%) patients. Other malignancies were lymphoma in 7/38 patients (18%), melanoma in 6/38 patients (16%), and leukemia in 4/38 patients (11%). Fig. 2 represents the distribution of first, second and recurrent malignancies.

In group B, the most common first malignancy was NMSC found in 15/48 (31%) patients. Other common malignancies in this group were colorectal cancer in 11/48 (23%) patients and melanoma in 6/48 (12.5%) patients.

Clinical outcomes

Second malignancies

After being diagnosed with their first malignancy, a total of 10/86 (9%) patients were further diagnosed with a second primary tumor. Of these, 5/10 (50%) patients were diagnosed with their first malignancy before IBD (i.e., were included in group A), and 5/10 (50%) were diagnosed with their first malignancy before IBD treatment was initiated (i.e., were included in group B). The median time from first to second malignancy was 7 years (IQR 16-6) and the median age of patients when diagnosed with the second primary

Table 1 Demographics, IBD classification and treatment exposure of patients with either second or recurrent malignancy

Characteristics	Second malignancy		Recurrent malignancy	
	No (N=76)	Yes (N=10)	No (N=66)	Yes (N=20)
Sex				
Male	45 (59%)	1 (10%)	36 (55%)	10 (50%)
Female	31 (41%)	9 (90%)	30 (45%)	10 (50%)
Smoking	26 (34%)	4 (40%)	23 (35%)	7 (35%)
IBD type				
Crohn's disease	53 (70%)	8 (80%)	46 (70%)	15 (75%)
Ulcerative colitis	23 (30%)	2 (20%)	20 (30%)	5 (25%)
Drug exposure				
Thiopurines	33 (43%)	7 (70%)	30 (45%)	10 (50%)
Methotrexate	7 (9%)	0 (0%)	4 (6%)	3 (15%)
Tofacitinib	3 (4%)	0 (0%)	3 (5%)	0 (0%)
Anti-TNF-α	26 (35%)	6 (60%)	21 (32%)	11 (55%)
Combination therapy*	10 (13%)	3 (30%)	12 (18%)	5 (25%)
Adalimumab	11 (14%)	2 (20%)	11 (17%)	2 (10%)
Infliximab	15 (20%)	4 (40%)	10 (15%)	9 (45%)
Vedolizumab	24 (32%)	6 (60%)	25 (38%)	5 (25%)
Ustekinumab	7 (9%)	3 (30%)	6 (9%)	4 (20%)

Values expressed as n (%). *Combination therapy: anti-TNF-α (either infliximab or adalimumab) in parallel with immunomodulator
IBD, inflammatory bowel disease; TNF, tumor necrosis factor

malignancy was 59 years (IQR 49-65). The most common second malignancy was NMSC, found in 6/10 (60%) patients, with lymphoma and leukemia in 3/10 (30%) and 1/10 (10%) patients, respectively. Female sex was found to be significantly associated with the risk for second malignancy (odds ratio [OR] 13.1, 95% confidence interval [CI] 2.29-247; P=0.017).

Malignancy recurrence

After documented confirmation of recovery from a first malignancy, 20/86 patients (23%) were found to have a relapse. Only 6/20 patients (30%) with recurrence of any malignancy were found to have first malignancy prior to IBD diagnosis. The median time from malignancy to recurrence was 3 years (IQR 9-3) and the most common recurrent malignancies were dermatologic: NMSC in 9/20 patients (45%), and melanoma in 3/20 patients (20%). Among the cases of recurrent NMSC, 5/20 patients (25%) and 4/20 patients (20%) had basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) of the skin, respectively. At the time of recurrence confirmation, 14/20 patients (70%) were on active treatment for IBD. Table 2 presents various IBD treatments and their potential association with second or recurrent malignancy. The only predictor found to be significantly associated with specific malignancy recurrence was treatment with infliximab, which was found to be associated with a higher risk of NMSC (OR 9.85, 95%CI 2.30-51.7; P=0.003). Table 3 shows different IBD treatments and association with different subtypes of recurrent malignancies. Fig. 3 demonstrates specific survival analysis for recurrent NMSC and the treatment with infliximab.

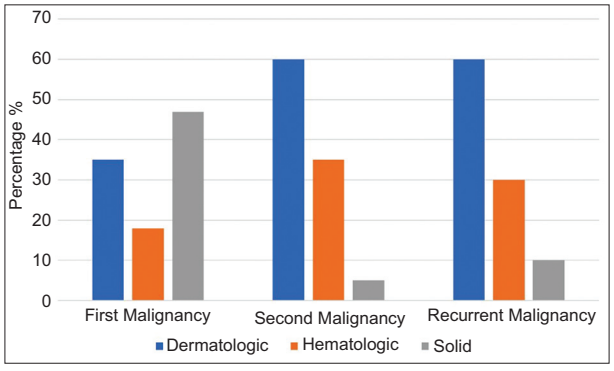

Figure 2 Subclasses of first, second and recurrent malignancies

Discussion

While the literature on primary malignancy and its associations with various immunosuppressive therapies is extensive, there is less data regarding the effect of immunosuppression on the risk of cancer recurrence or the development of a new primary neoplasm. In our opinion, the most important finding of this study is that monotherapy with infliximab, a TNF-α blocker, is associated with an increased risk of malignancy recurrence, specifically NMSC.

This finding is in contrast to the findings of a large multicenter prospective study by the CESAME group, which did not find an association between exposure to immunosuppressants and the risk for NMSC recurrence, among other malignancies that were tested. However, it is worth mentioning that the conclusions of that study did not apply to anti-TNF therapies, because of the small number of patients exposed to those drugs [6]. Likewise, further studies published by Axelrad *et al* and Waljee *et al* did not identify an increased risk for new or recurrent cancers among IBD patients receiving immunosuppression with anti-TNF monotherapy or combination therapy [7,10].

A large network meta-analysis included 16 studies of patients with immune-mediated diseases, including IBD, and previous malignancy found no increased risk for recurrent cancers with conventional immunosuppressants or anti-TNF agents. However, in the case of combination therapy, there were signs of a trend towards higher risk that did not reach statistical significance [8]. In our study, only a very small number of patients were on combination therapy with anti-TNFs and immunomodulator, as well as vedolizumab or ustekinumab; thus, we could not draw meaningful conclusions regarding these treatments.

Table 2 Correlation of IBD therapy and second or recurrent malignancy

Characteristics	Second malignancy (N=10)				Recurrent malignancy (N=20)			
	N (%)	OR	95%CI	P-value	N (%)	OR	95%CI	P-value
Female sex	9 (90%)	13.1	2.29-247	0.017	7 (35%)	1.20	0.44-3.30	0.72
Drug Exposure								
Thiopurines	7 (70%)	3.04	0.78-14.9	0.13	10 (50%)	1.20	0.44-3.30	0.72
Methotrexate	0 (0%)	0.00	0.74-11.9	>0.99	3 (15%)	2.74	0.50-13.6	0.21
Tofacitinib	0 (0%)	0.00	0.36-5.22	>0.99	0 (0%)	0.00	0.92-7.29	>0.99
Anti-TNF-α	6 (60%)	2.83	0.21-6.92	0.13	11 (55%)	2.56	0.24-3.89	0.07
Combination therapy*	2 (20%)	1.68	0.63-10.8	0.78	2 (10%)	1.89	0.08-2.33	0.56
Adalimumab	2 (20%)	1.48	0.85-13.7	0.65	2 (10%)	0.56	1.51-14.2	0.47
Infliximab	4 (40%)	2.71	0.78-19.5	0.16	9 (45%)	4.58	0.16-1.61	0.007
Vedolizumab	6 (60%)	3.25		0.09	5 (25%)	0.55	0.58-9.86	0.29
Ustekinumab	3 (30%)	4.22		0.07	4 (20%)	2.50		0.19

*Combination therapy: anti-TNF-α (either infliximab or adalimumab) in parallel with immunomodulator

IBD, inflammatory bowel disease; TNF, tumor necrosis factor; OR, odds ratio; CI, confidence interval

Table 3 Correlation of IBD therapy and specific recurrent malignancies

Recurrent malignancy	Treatment	N (%)	OR	95%CI	P-value
Non-melanoma skin cancer (N=9)	Thiopurines	6 (67%)	2.53	0.62-12.7	0.21
	Methotrexate	1 (11%)	1.48	0.07-10.3	0.73
	Tofacitinib	0 (0%)	0.00		>0.99
	Anti-TNF-α	8 (89%)	7.14	1.59-50.3	0.012
	Combination therapy*	1 (11%)	1.23	0.06-8.54	0.64
	Adalimumab	1 (11%)	0.68	0.03-4.21	0.72
	Infliximab	7 (78%)	9.85	2.30-51.7	0.003
	Vedolizumab	4 (44%)	1.57	0.36-6.42	0.53
	Ustekinumab	3 (33%)	5.00	0.91-24.0	0.047
Melanoma (N=3)	Thiopurines	1 (33%)	0.56	0.03-6.11	0.65
	Methotrexate	1 (33%)	6.42	0.28-77.4	0.15
	Tofacitinib	0 (0%)	0.00		>0.99
	Anti-TNF-α	2 (67%)	3.47	0.32-76.5	0.32
	Combination therapy*	0 (0%)	0.00		>0.99
	Adalimumab	1 (33%)	2.96	0.13-33.3	0.39
	Infliximab	2 (67%)	7.76	0.70-173	0.10
	Vedolizumab	1 (33%)	0.93	0.04-10.1	0.95
	Ustekinumab	1 (33%)	4.11	0.18-47.3	0.27
Lymphoma (N=3)	Thiopurines	0 (0%)	0.00		>0.99
	Methotrexate	1 (33%)	6.42	0.28-77.4	0.15
	Tofacitinib	0 (0%)	0.00		>0.99
	Anti-TNF-α	1 (33%)	0.00		>0.99
	Combination therapy*	1 (33%)	5.54	0.15-70.2	0.18
	Adalimumab	0 (0%)	0.00		>0.99
	Infliximab	1 (33%)	0.00		>0.99
	Vedolizumab	0 (0%)	0.00		>0.99
	Ustekinumab	0 (0%)	0.00		>0.99
Leukemia (N=3)	Thiopurines	1 (33%)	2.37	0.22-52.1	0.49
	Methotrexate	1 (33%)	2.37	0.22-52.1	0.49
	Tofacitinib	0 (0%)	0.00		>0.99
	Anti-TNF-α	0 (0%)	0.00		>0.99
	Combination therapy*	0 (0%)	0.00		>0.99
	Adalimumab	0 (0%)	0.82	0.04-8.93	0.88
	Infliximab	0 (0%)	0.00		>0.99
	Vedolizumab	0 (0%)	1.81	0.08-19.9	0.64
	Ustekinumab	0 (0%)	0.00		>0.99
Solid (N=2)	Thiopurines	1 (50%)	4.32	0.86-5.15	0.73
	Methotrexate	0 (0%)	0.00		>0.99
	Tofacitinib	0 (0%)	0.00		>0.99
	Anti-TNF-α	2 (100%)	6.64	0.59-12.54	0.32
	Combination therapy*	0 (0%)	0.00		>0.99
	Adalimumab	0 (0%)	0.00		>0.99
	Infliximab	2 (100%)	6.64	0.59-12.54	0.32
	Vedolizumab	0 (0%)	0.00		>0.99
	Ustekinumab	0 (0%)	0.00		>0.99

*Combination therapy: anti-TNF-α (either infliximab or adalimumab) in parallel with immunomodulator

IBD, inflammatory bowel disease; TNF, tumor necrosis factor; OR, odds ratio; CI, confidence interval

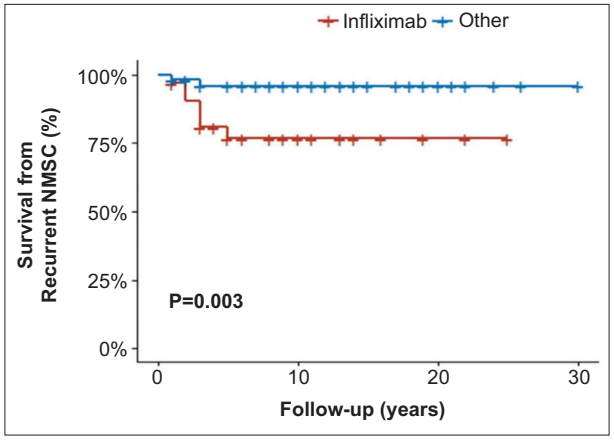

Figure 3 Kaplan-Meier survival analysis shows plot of cumulative events for treatment with infliximab and recurrent non-melanoma skin cancer (NMSC)

When widening the search for evidence, malignancy secondary to therapy-related immunosuppression seems to be better described in the context of other inflammatory diseases than IBD, for example, RA. Various retrospective studies of patients with RA demonstrated no difference in the development of new or recurrent cancer in patients with prior malignancy who were subsequently exposed to anti-TNFs, compared with those receiving disease-modifying antirheumatic drugs alone [11].

Skin cancers, including melanoma and non-melanoma cancers, are increasing in the western world, with recent data showing a progressively increasing incidence of NMSC over the last 2 decades [12]. The increasing burden of IBD and NMSC prevalence, together with increasing life expectancy, may cause treatment dilemmas, whereby physicians need to weigh the risk for cancer recurrence against specific therapies with potential to better control IBD activity [13]. This challenge may be further amplified when considering immunosuppressive therapy in elderly patients with IBD and previous cancer, given that age is an important and independent risk factor for the development of various malignancies [14] and opportunistic infections [15,16].

Although evidence regarding the general effect of cancer on IBD activity is limited, past studies have suggested that cancer in the presence of chronic inflammatory disease such as IBD may have further impact on fundamental clinical decisions, such as the choice of the most suitable IBD-targeted drug for each individual patient [17]. From the findings of our study, it appears that there might be potential safety concerns when biologics such anti-TNFs are being considered as a potential treatment strategy for patients with prior NMSC.

Additional interesting findings of this study are within the area of primary malignancy. The rate of primary malignancy in IBD patients varies between studies. A recent study from a nationwide Swiss registry demonstrated a rate of 3.9% of IBD patients diagnosed with at least one malignancy [18]. Interestingly, in our preliminary cohort, this equivalent rate was more than tripled. We hypothesize that a reasonable explanation for this observation may be that our cohort was comprised of tertiary care patients for both IBD and oncology.

We acknowledge several limitations of the current study that are inherent to its retrospective design. Our analysis cannot prove cause-and-effect relationships between immunosuppression and new or recurrent cancer in patients with both IBD and a history of malignancy. The observed associations could have been due to individualized decision-making in IBD management, or the presence of factors that contribute to cancer development: chronic medical conditions (irrespective of IBD) managed and followed outside the hospital and were not included in our database, or current smoking or a history thereof, which was documented in the vast majority of patients. Additionally, the relatively small sample size, together with the potential for misclassification because of incomplete capture of patient's malignancy data, suggests that the conclusions of this study may not be generalizable to other clinical settings and further research is obligatory.

Despite these limitations, this study has shown that, among patients with an existing malignancy before initiation of immunosuppressive treatment, exposure to anti-TNF medications was indeed associated with an increased risk for NMSC recurrence compared with patients who did not receive these agents.

In conclusion, this study showed that treatment with infliximab is associated with an increased risk for NMSC recurrence in patients with IBD. We acknowledge on the one hand that our finding contradicts the findings of larger studies, but it underscores the importance of rigorous dermatological follow up of IBD patients with previous NMSC treated with anti-TNFs, specifically infliximab. It is important to stress that larger and prospective studies are needed for better understanding of the association of immunosuppressive therapy and the potential risk for malignancy recurrence.

Summary Box

What is already known:

- Patients with inflammatory bowel disease (IBD) have a high overall risk for primary malignancy
- IBD-related immunosuppressive therapy such azathioprine may increase the risk for certain primary malignancies
- The link between biologics and primary, secondary or recurrent malignancies is controversial

What the new findings are:

- Treatment with tumor necrosis factor-α inhibitors for IBD may be associated with the risk for recurrence of non-melanoma skin cancer (NMSC)
- Female sex is associated with the risk for second malignancy in patients with IBD
- Rigorous dermatological follow up of IBD patients with prior NMSC is mandatory

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