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Increased Risk for Non-Melanoma Skin Cancer in Patients with Inflammatory Bowel Disease

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Abstract

Background & Aims—Patients with inflammatory bowel disease (IBD) might be at increased risk for certain malignancies. We evaluated the risk of non-melanoma skin cancer (NMSC) in patients with IBD and determined how immunosuppressive and biologic medications affect this risk.

Methods—We performed retrospective cohort and nested case-control studies using administrative data from PharMetrics Patient Centric Database. In the cohort study, 26403 patients with Crohn's disease (CD) and 26974 patients with ulcerative colitis (UC) were each matched to 3 non-IBD controls. NMSC risk was evaluated by incidence rate ratio. In the nested case-control study, 387 CD patients and 355 UC patients with NMSC were each matched to 4 IBD patients without NMSC using incidence density sampling. Conditional logistic regression was used to determine the association between specific IBD medication use and NMSC.

Results—In the cohort study, the incidence of NMSC was higher among patients with IBD compared to controls (incidence rate ratio [IRR] 1.64, 95% confidence interval [CI] 1.51–1.78). In the nested-case control study, recent thiopurine use (≤ 90 days) was associated with NMSC (adjusted odds ratio [OR] 3.56, 95% CI 2.81–4.50), as was recent biologic use among patients with CD (adjusted OR 2.07, 95% CI 1.28–3.33). Persistent thiopurine use (> 365 days) was associated with NMSC (adjusted OR 4.27, 95% CI 3.08–5.92), as was persistent biologic use among patients with CD (adjusted OR 2.18 95% CI 1.07–4.46).

Conclusions—Patients with IBD, especially those that receive thiopurines, are at risk for NMSC. Appropriate counseling and monitoring of such patients with IBD is recommended.

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Keywords

inflammatory bowel disease; non-melanoma skin cancer; immunosuppression; thiopurines; anti-TNF

Introduction

One in five Americans develops skin cancer, which accounts for one third of all cancers in the United States.¹ In fact, non-melanoma skin cancer (NMSC) is one of the most common types of cancer in lighter skin type populations. There were over a million cases of NMSC diagnosed in 2008. The causes of NMSC are multifactorial, including both environmental and host factors. Known environmental risk factors for NMSC include sun exposure (ultraviolet (UV) light), chemical exposures and ozone depletion. Host risk factors include human papilloma virus, genetic susceptibilities, skin tone and immunosuppression.² NMSC incidence increases with decreasing latitude, thereby demonstrating the profound risk of sun exposure.³

Patients with inflammatory bowel disease (IBD) may be at increased risk for NMSC, either related to the immunosuppressive medications used to treat the disease and/or underlying altered regulation of the immune system. In studies of patients post organ transplant on immunosuppressive medications, there is a markedly increased risk of SCC that correlates with degree of immunosuppression.^{4–6} For this reason, routine skin examination is performed in post-transplant populations. Fewer studies have focused on NMSC risk in patients with IBD who use immunosuppressive medications,^{7–9} and guidelines for skin cancer screening and prevention are not included in current practice guidelines for IBD.

The specific aims of this study were 1) to evaluate the risk of NMSC in patients with and without IBD and 2) to evaluate the risk of NMSC in patients with IBD who use immunosuppressive medications or biologic anti-tumor necrosis factor (anti-TNF) therapies as compared to IBD patients who do not use these medications.

Materials and Methods

Data Source

We analyzed the procedural and outpatient pharmaceutical insurance claims contained in the PharMetrics Patient-Centric Database (IMS Health, Watertown, MA) for the period August 1, 1996 through June 30, 2005. This longitudinal, patient-level database has been used in previous epidemiological studies of IBD.^{10, 11} The included plans capture a geographically diverse sample. The number of plans per major U.S. census region (East, South, Midwest, West) ranges from 12–34 and the number of states represented per region ranges from 5–10. The database contains information on over 9 million enrollees, with anywhere from 19,000 to 3.6 million (mean, 992,000) enrollees per state. At the time of this study, the database included claims from 87 health plans in 33 states. Prior studies have reported PharMetrics to be representative of the national commercially-insured population on a variety of demographic measures, including geographic region, age, gender, and health plan type.¹²

Study Design

We performed a retrospective cohort study to determine the overall risk of NMSC in IBD patients compared to non-IBD controls, and a nested-case control to determine the independent effects of medication use (immunosuppressive and anti-TNF therapy) on NMSC among patients with IBD. A similar design has previously been used by Gupta et al to evaluate the

incidence of herpes zoster in patients with IBD and the effects of various medication exposures.¹³

Cohort Study

Patient selection—All patients aged <64 with at least 6 months of continuous health plan enrollment were eligible for inclusion in this analysis. We chose 64 as the upper age limit to avoid the possibility of missing data resulting from Medicare dual eligibility (which begins at age 65). We identified cases of Crohn's disease (CD) and ulcerative colitis (UC) using a previously reported administrative definition.¹⁰ This definition included patients with at least 3 health care contacts, on different days, associated with an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) diagnosis code for CD (555.xx) or UC (556.xx), or patients with at least one claim for CD or UC and at least 1 pharmacy claim for any of the following medications: mesalamine, olsalazine, balsalazide, sulfasalazine, 6-mercaptopurine, azathioprine, infliximab, adalimumab, and enteral budesonide. For patients who had claims for both CD and UC, disease assignment was made according to the majority of the last 9 claims, or the majority of total claims if there were fewer than 9.

We matched each IBD patient to 3 control subjects by age, gender, U.S. census region, and length of enrollment. Region of the country was defined by standard regional definitions from the United States Census Bureau. The outcome of NMSC was only assessed after at least 3 months of exposure time within the cohort to minimize the inclusion of prevalent cases.

Assessment of outcome (non melanoma skin cancer)—The primary outcome of interest was first diagnosis of NMSC identified by either 1) a claim containing a Current Procedural Terminology, 4th edition (CPT-4) code for interpretation of pathology from an office or surgical setting (88301-88309 and/or 88329-88332) and an International Classification of Diseases, 9th revision (ICD-9) diagnosis code of NMSC (173.0–173.9 or 232.0–232.9), or 2) a claim containing a CPT-4 code for destruction or excision (116xx, 172xx, 17300-17310) and one of the previously mentioned ICD-9 codes of NMSC. Pathology CPT codes and ICD-9 diagnosis codes were used to identify cases of NMSC in a previous epidemiological study of administrative data.¹⁴

Assessment of follow-up time interval—For each IBD patient, the follow up period began with the 1st claim with a diagnosis code defining CD or UC. For controls, follow up began on the first day of health plan eligibility. Follow up continued until whichever of the following occurred first: diagnosis of NMSC, death, discontinuation of insurance coverage or age >65.

Statistical Analysis—We used descriptive statistics to summarize characteristics of cases and controls. Continuous variables are reported as mean $\pm$ standard deviation (SD) and categorical variables are reported as percentages. We then calculated incidence rates of NMSC (per 100,000 person-years) and used incidence rate ratios (IRRs) and 95% confidence intervals to compare the incidence of NMSC in IBD patients and controls. We also performed subsequent analyses, stratifying by region of the country (defined by United States census groups), age (in decades), and disease type (UC versus CD).

Nested Case-Control Study

We next conducted a case-control study evaluating the association between immunosuppressive or biologic anti-TNF medication use and NMSC. This study was nested within the previously defined cohort of patients with IBD.

Selection of Cases and Controls—Cases were those IBD patients who were diagnosed with NMSC and controls were those IBD patients without NMSC. Each case patient was matched on gender, age, geographic region, disease type (CD or UC) and duration of follow-up to 4 IBD patients who did not have NMSC using incidence density sampling.¹⁵ In this sampling technique, a case patient can also be a control patient, provided that the case patient has not yet been diagnosed with NMSC (has not yet become a case) at the time he or she is selected as a control. Once a case is diagnosed with NMSC, he or she is no longer eligible to become a control. A total of 172 patients were included as both cases and controls. Each control was assigned an index date whereby his or her corresponding length of observation time prior to that date was equal to the observation time of the matched case prior to the diagnosis of NMSC.

Assessment of exposures (medication use)—The primary medications evaluated included: azathioprine and 6-mercaptopurine (thiopurine class), methotrexate, tacrolimus and cyclosporine (calcineurin class), mycophenolate mofetil (MMF), infliximab and adalimumab (biologic class). Corticosteroids were not included in our analysis due to varying indications for use and varying length of therapy associated with each prescription. Medication exposures were analyzed with respect to amount of time preceding the diagnosis of NMSC in cases, or the corresponding index date in controls. “Recent” exposures were defined as at least one outpatient pharmacy claim occurring in the 90 days prior to NMSC diagnosis. “Persistent” use was defined as at least one outpatient pharmacy claim occurring in the 90 days prior to NMSC diagnosis and at least one outpatient pharmacy claim occurring greater than 365 days prior to NMSC diagnosis. Accordingly, persistent medication use was only assessed for those patients whose NMSC (cases) or index date (controls) occurred >365 days from the beginning of the follow up period.

Statistical analysis—Characteristics of cases and controls were described using the same methods as in the cohort study. We then used conditional logistic regression to calculate odds ratios (OR) and 95% confidence intervals for each medication exposure related to the outcome of NMSC. We constructed a full model using all potential confounders and eliminated these confounders via a backwards elimination strategy, using a change in estimate approach. The only confounders of these associations were the other medication group (i.e. other immunosuppressive medications were a confounder of the association between biologic anti-TNF agents and NMSC, the inverse was also true). Analyses were performed for patients with IBD and also stratified by UC and CD diagnosis. In the case of methotrexate use and biologic use, these analyses were only performed for patients with CD. Methotrexate is not commonly used in the treatment of UC in the United States and at the time these data were obtained, the FDA had not yet approved infliximab for UC. Analyses of combined immunosuppression use (immunomodulator and biologic) were also only performed in patients with CD.

For all analyses, p-values were two-sided, and a p-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using Stata version 9.0 (Texas Station, TX). Analyses were performed for patients with IBD and also stratified by UC or CD diagnosis. The study protocol was granted exemption from review by the Institutional Review Board at University of North Carolina because it involved the use of existing, de-identified data.

Results

Cohort Study

The study population for the cohort study included 53377 patients with IBD. Of these, 26403 had CD and 26974 had UC. The median length of follow-up within this cohort was 730 days

(interquartile range 456–1004) for CD patients, 700 days (interquartile range 456–988) for UC patients and 1004 days (interquartile range 730–1217) for controls. Characteristics of the patients with IBD were well matched to their controls (Table 1).

For patients with IBD, the overall annual incidence rate of NMSC was 733 cases per 100,000. The overall annual incidence rate of NMSC for controls was substantially lower (447 cases of NMSC per 100,000). The incidence of NMSC for both patients with CD or UC, and their matched controls, was highest in the South compared to other regions of the country (Supplementary Figure 1). When IBD patients were compared to their matched controls, the incidence rate ratio for NMSC was significantly higher for patients with IBD (IRR 1.64 95% CI 1.51–1.78). The same was true when this was evaluated by disease sub-type (CD IRR 1.84, 95% CI 1.63–2.06, UC IRR 1.47, 95% CI 1.31–1.65). There were no important differences in the incidence rate ratios by region (data not shown).

Nested Case-Control Study

The study population for the nested case-control study of IBD patients included 742 cases of NMSC and 2968 matched controls. Age, gender, region, type of IBD, and time at risk did not differ between cases and controls (Table 2). Differences in medication use are demonstrated in Table 3. The cases had significantly greater recent use of thiopurines and recent use of any non-biologic immunomodulator. For patients with CD, the cases also had greater recent use of biologic anti-TNF agents.

In adjusted analyses, recent thiopurine use in particular (adjusted OR 3.56 95% CI 2.81–4.50) and any recent immunosuppressive medication use (adjusted OR 3.28 95% CI 2.62–4.10) were associated with NMSC. Among patients with CD, those who recently used biologic medications also had increased odds of developing NMSC (adjusted OR 2.07 95% CI 1.28–3.33) (Table 4). Patients with CD who recently used combined therapy (immunomodulator and biologic) had increased odds of NMSC when compared to those using no medications (adjusted OR 5.85 95% CI (3.2–10.8)) (Table 5).

We next analyzed persistent medication use in those patients with >365 days of follow-up prior to their (or their matched case's) diagnosis of NMSC. This population included 452 cases of skin cancer and 1812 matched controls. Rates of persistent medication use by cases and controls are demonstrated in Table 3. Again, cases had significantly greater thiopurine use and any immunomodulator use. For those patients with CD, cases had greater biologic use when compared to controls. In adjusted analyses, persistent thiopurine use (adjusted OR 4.27 95% CI 3.08–5.92) and any persistent immunosuppressive medication use (adjusted OR 4.04 95% CI 2.96–5.53) were associated with NMSC. Among patients with CD patients, persistent biologic medication use was associated with NMSC (adjusted OR 2.18 95% CI 1.07–4.46) (Table 4). Those who persistently used combined therapy (immunomodulator and biologic) also had an increased odds of NMSC when compared to no medication use (adjusted OR 6.75 95% CI 2.74–16.65) (Table 5).

Discussion

This study demonstrates that inflammatory bowel disease patients have an increased risk of NMSC (IRR 1.64 95% CI 1.51–1.78). This risk may be attributed, in part, to the underlying immune dysfunction of IBD, although the use of immunosuppressive medications appears to be a key driver as well. In particular, we observed that IBD patients with long term use of thiopurines, other immunosuppressive agents, and patients with CD on anti-TNF medications or a combination of anti-TNF and immunosuppressive medications appear to be at the highest risk of developing NMSC. The findings presented in this study strongly suggest that NMSC

can be considered a potential adverse effect of many IBD treatments, and should be considered when weighing the risks and benefits of different therapeutic approaches.

A similar association between immunosuppressive use and NMSC in patients post solid-organ transplant has also been demonstrated.¹⁶ Squamous cell and basal cell skin cancers account for more than 90% of all skin cancers in post-transplant patients.^{6, 17} The risk of SCC is 65 to 250 times more common in transplant recipients than in the general population.⁶ Both duration and level of immunosuppression have been positively associated with NMSC. Over 80% of transplant recipients have developed SCC 20 years post transplant, demonstrating the cumulative effects of long-term immunosuppression.¹⁸ The magnitude of the association between immunosuppressant use and NMSC observed in this study was less than that observed in transplant recipients, perhaps related to lesser degrees of immunosuppression in IBD patients and/or the exclusion of patients ≥ 64 years of age in our study.

Few previous studies have evaluated the risk of NMSC in patients with IBD. In a Danish study, patients with UC were found to have an increased risk of NMSC (RR 1.4, 95% CI 1.0–1.9).⁷ A second Swedish study of patients with IBD demonstrated an increased risk of squamous cell skin cancer (SIR 2.2 95% CI 1.1–3.9).⁸ Both of these studies did not have access to data on medication exposures and were performed in Northern European populations, where skin type and susceptibility to sun exposure may be different than that in the United States. Our study also permitted further identification of risk factors for NMSC, including geographical region (a proxy for sun exposure) and use of immunosuppressive medications.

Although immunosuppressive use in general has been previously associated with NMSC, to our knowledge this is the first epidemiological study to describe an association between NMSC and use of biologic therapies, specifically anti-TNF agents in patients with IBD. However, this association has been suggested in case-reports of patients with rheumatoid arthritis (RA) treated with biologic therapies.¹⁹ Additionally, a meta-analysis of the side-effects of anti-TNF agents in the rheumatology population did find an overall increased risk of malignancy (pooled OR 3.3 (95% CI, 1.2–9.1)).²⁰ Chakravarty et al demonstrated that patients with RA treated with anti-TNF agents alone or in combination with methotrexate have an increased risk of NMSC.²¹ In contrast to rheumatologic disease, anti-TNF medications have not previously been associated with an increased risk of malignancy in patients with IBD.^{22,23} Until now, little was known about the risk of NMSC in patients with IBD treated with anti-TNF agents or the combination of anti-TNF agents and other immunosuppressive medications.

An interesting observation in our study was that the risk of NMSC seems to be greatest among thiopurine (6MP/azathioprine) users. This finding is consistent with previous work demonstrating that azathioprine can increase photosensitization of human skin.²⁴ Patients treated with azathioprine have a reduced minimal erythema dose (lowest amount of radiation required to produce erythema 24 hours after irradiation) for UVA light, but not UVB light.²⁴ The selective sensitivity to UVA in azathioprine treated patients is consistent with the production of 6-thioguanine DNA photoproducts. UVA light makes up a majority of incident midday solar radiation, is able to penetrate through glass and is present throughout the year.²⁵ Therefore, many patients would be exposed to this harmful radiation inadvertently. However, the carcinogenic effects of ultraviolet radiation are thought to be mostly caused by UVB rather than UVA exposure.²⁵ This underscores the need for further studies which elucidate the biological mechanism responsible for this association.

The most significant strengths of this study include the large sample size and geographic diversity of the study population, as well as the ability to assess both exposures and outcomes in both the inpatient and outpatient settings. By drawing from a large number of health plans of varying size, type, and location throughout the United States, we believe these results to be

broadly generalizable. Another strength of this study was the ability to use pharmacy claims to assess medication exposure, rather than relying on patient recall and/or medical records which indicate medications prescribed (although not necessarily filled).

This study also has some limitations that merit consideration. First, as with all epidemiologic studies using administrative data, there is always the possibility of misclassification of exposure and outcome related to the lack of clinical detail. To minimize this risk, we used stringent definitions of both exposures and outcomes. Similar previous administrative definitions of IBD have been used by our group,^{10, 11} and others.²⁶ The administrative definition of NMSC consisting of an ICD-9 diagnosis code in association with a pathology CPT code has also been used previously.¹⁴ Due to overlapping ICD-9 codes, we were unable to distinguish between basal cell and squamous cell skin cancers. Thus, the outcome was classified as NMSC.

Another limitation to this study is that although our data source is generalizable to the commercially insured population of the United States, the elderly and uninsured were not represented in our population. To the extent that NMSC incidence increases with age, we may have underestimated the overall incidence of this condition. However, this would not affect the estimates of risk observed in our study, as measured by incidence rate ratios. Additionally, our database did not contain data on race or ethnicity. Race could be an unmeasured confounder if it is associated with both the outcome and the exposure. Race is associated with the outcome of NMSC. Race may or may not be associated with our exposures of IBD (in the cohort study) and immunosuppressive medication use (in the nested case-control study). Several studies suggest that the incidence of IBD among African Americans is approaching that of Caucasians. Among studies that have shown differences in immunosuppressive medication use by race,²⁷ many quote access to care and socioeconomic factors as a potential cause. In our study, all patients are insured and have access to care, thereby alleviating many of the socioeconomic factors.

A potential source of bias in the cohort portion of this study could be detection bias, either due to increased health care contact by patients with IBD and/or lower thresholds for referral for biopsy of suspicious skin lesions. The incidence rate of NMSC in our control group was 447 per 100,000. The incidence rate of NMSC in the US is in the range of 333–433 per 100,000. Therefore, detection bias in the control group is likely relatively small. Additionally, we included only insured patients, so access to care should be similar. Detection bias is less likely to have occurred in the case-control study, as our IBD definition required both access to and utilization of health care resources. A final limitation is that information regarding potential confounders, such as smoking and sun exposure, are not available in administrative data. However, our analysis was matched on region, as a proxy for sun exposure. Smoking alone is unlikely to have caused the robust effect estimates observed in this study.

In summary, we have demonstrated an increased incidence of NMSC in patients with IBD, and especially among those on immunosuppressive medications such as thiopurines and to a lesser extent, patients with CD on anti-TNF medications. Given the increased use of these steroid-sparing regimens by IBD patients and the potential for decades of exposure time, we anticipate that the risks presented here will be magnified in years ahead. The findings in this study have important implications for skin cancer screening and prevention. Although definitive recommendations should be based not only on disease risk, but also on the benefits, harms, and costs of screening and ultimate treatment, this study represents an important first step in the development of prevention programs for patients with IBD. Such programs might include behavior alterations such as sun avoidance and/or increased use of sun protective clothing and broad spectrum sunscreen. Education for patients with IBD in regards to the increased risk of NMSC associated with immunosuppressive medication use is also needed in order to change

behaviors. Finally, there may also be a role for skin cancer screening programs, including full skin examinations performed at regular intervals by trained dermatologists.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NMSC	non-melanoma skin cancer
IBD	inflammatory bowel disease
UC	ulcerative colitis
CD	Crohn's disease
anti-TNF	anti-tumor necrosis factor alpha
ICD-9	International Classification of Diseases, 9 th revision
CPT-4	Current Procedural Terminology, 4 th edition
RA	rheumatoid arthritis

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Table 1

Characteristics of the Study Population (Cohort Study): Patients with IBD and Controls matched by age (within 3 years), region of the country, and gender

	CD (n=26403)	UC (n=26974)	Controls (n=160037)
Female gender (%)	14842 (56.2%)	14174 (52.6%)	87000 (54.4%)
Region of the country (%)			
East	6379 (24.2%)	6937 (25.7%)	39927 (25.0)
Midwest	9462 (35.8%)	8949 (33.2%)	55189 (34.5)
South	6243 (23.7%)	6044 (22.4%)	36840 (23.0)
West	4319 (16.4%)	5044 (18.7%)	28081 (17.5)
Median time in cohort (days), (interquartile range)	730 (456–1004)	700 (456–988)	1004 (730–1217)
Mean age at cohort entry, (standard deviation)	39.1 (13.5)	41.5 (12.7)	39.7 (13.2)
Medicaid insurance (%)	621 (2.4%)	361 (1.3%)	3397 (2.1%)

Table 2

Characteristics of the cases of NMSC with IBD and matched controls with IBD in nested case-control study, matched by CD or UC, age (within 3 years), gender, and region of the country

	Cases (n=742)		Controls (n=2968)	
Gender (n, %)				
Female	n=353	47.6%	n=1412	47.6%
Male	n=389	52.4%	n=1556	52.4%
Mean age at IBD diagnosis (start of follow up), SD	n=742	49.7 (8.7)	n=2968	49.2 (9.4)
Median time at risk, days (interquartile range)	n=742	483.5 (266–777)	n=2968	483.5 (266–777)
IBD diagnosis				
CD, n (%)	n=387	52.2%	n=1548	52.2%
UC, n (%)	n=355	47.8%	n=1420	47.8%
Region of the country				
East	n=157	21.2%	n=628	21.2%
Midwest	n=189	25.5%	n=756	25.5%
South	n=253	34.1%	n=1012	34.1%
West	n=143	19.3%	n=572	19.3%
Medicaid (%)	n=2	0.3%	n=55	1.9%

Recent and Persistent* medication use by the cases of NMSC with IBD and matched controls with IBD in nested case-control study, matched by CD or UC, age (within 3 years), gender and region of the country

Table 3

Recent Use (≤90 days)	Medication class	Cases n=742		Controls n=2968		P value
		No.	%	No.	%	
	Biologic [¶]	n=38	5.1%	n=63	2.1%	<0.01
	Thiopurine	n=168	22.6%	n=236	8.0%	<0.01
	Methotrexate	n=9	1.2%	n=22	0.7%	0.21
	Calcineurin inhibitor [§]	n=8	1.1%	n=17	0.6%	0.13
	MMF [^]	n=2	0.3%	n=5	0.2%	0.57
	Any immunomodulator ^{**}	n=182	24.5%	n=274	9.2%	<0.01

Persistent Use (>365 days)	Medication class	Cases n=452		Controls n=1812		P value
		No.	%	No.	%	
	Biologic [¶]	n=19	4.2%	n=26	1.4%	<0.01
	Thiopurine	n=93	20.6%	n=114	6.3%	<0.01
	Methotrexate	n=6	1.3%	n=9	0.5%	0.05
	Calcineurin inhibitor [§]	n=3	0.7%	n=7	0.4%	0.43
	MMF [^]	n=2	0.4%	n=2	0.1%	0.13
	Any immunomodulator ^{**}	n=103	22.8%	n=130	7.2%	<0.01

* Only those with >365 days of exposure time prior to NMSC or index date were included in analyses of persistent medication use

[¶] Adalimumab or infliximab

[§] Tacrolimus or Cyclosporine

[^] Mycophenolate mofetil

^{**} Thiopurine class, calcineurin inhibitor, mycophenolate mofetil, methotrexate

Table 4

Crude and Multivariate Analyses of Recent and Persistent* Medication Use and Non-Melanoma Skin Cancer in Patients with IBD, overall and by CD or UC

Recent Use (≤ 90 days)	IBD, overall (n=3710)		Crohn's Disease (n=1935)		Ulcerative Colitis (n=1775)	
	Crude OR, 95% CI	Adjusted [^] OR, 95% CI	Crude OR, 95% CI	Adjusted OR, 95% CI	Crude OR, 95% CI	Adjusted [^] OR, 95% CI
Thiopurine	3.65, (2.90–4.60)	3.56, (2.81–4.50)	3.99, (2.99–5.33)	3.87, (2.88–5.21)	3.13, (2.13–4.59)	3.09, (2.10–4.54)
Methotrexate	N/A	N/A	1.62, (0.62–4.24)	1.58, (0.57–4.33)	**	**
Calcineurin inhibitor [§]	1.88, (0.81–4.36)	1.50, (0.60–3.76)	2.00, (0.60–6.64)	1.48, (0.37–5.97)	1.78, (0.55–5.77)	1.52, (0.45–5.14)
Any immuno-modulator [†]	3.42, (2.75–4.26)	3.28, (2.62–4.10)	3.73, (2.83–4.93)	3.53, (2.66–4.70)	2.95, (2.06–4.24)	2.94, (2.06–4.24)
Any Biologic [¶]	N/A	N/A	2.63, (1.70–4.08)	2.07, (1.28–3.33)	#	#

Persistent Use (> 365 days)	IBD, overall (n=2264)		Crohn's Disease (n=1141)		Ulcerative Colitis (n=1123)	
	Crude OR, 95% CI	Adjusted [^] OR, 95% CI	Crude OR, 95% CI	Adjusted OR, 95% CI	Crude OR, 95% CI	Adjusted [^] OR, 95% CI
Thiopurine	4.36, (3.16–6.02)	4.27, (3.08–5.92)	4.46, (2.97–6.70)	4.25, (2.81–6.42)	4.19, (2.46–7.15)	4.34, (2.53–7.43)
Methotrexate	N/A	N/A	2.83, (1.00–15.99)	2.69, (0.63–11.56)	**	**
Calcineurin inhibitor [§]	1.71, (0.44–6.63)	1.53, (0.28–8.43)	1.33, (0.14–12.82)	1.76, (0.18–17.24)	2.00, (0.37–10.92)	2.81, (0.50–15.9)
Any immuno-modulator [†]	4.28, (3.15–5.82)	4.04, (2.96–5.53)	4.53, (3.06–6.69)	4.16, (2.79–6.19)	3.90, (2.36–6.43)	3.96, (2.38–6.58)
Any Biologic [¶]	N/A	N/A	3.51, (1.81–6.81)	2.18, (1.07–4.46)	#	#

* Only those with >365 days of exposure time prior to NMSC or index date were included in analyses of persistent medication use

[^] Adjusted for other classes of medications and Medicaid insurance status

** Methotrexate is not indicated for the treatment of ulcerative colitis in the United States

[§] Tacrolimus or cyclosporine

[†] Thiopurine class, calcineurin inhibitor, mycophenolate mofetil, methotrexate

[¶] Adalimumab or infliximab

Infliximab approved for UC in September 2005 in the United States, after collection of these data. Adalimumab is not approved for the treatment of UC in the United States.

Table 5

Association of Recent and Persistent* Immunosuppressive Medication Combinations with Non-Melanoma Skin Cancer Among Patients with Crohn's Disease

Recent Use (≤90 days)	Cases (n=387)	Controls (n=1548)	OR (95% CI) [^]	p value
None	250 (65%)	1331 (86%)	1.0 (reference)	
Any immunomodulator**	101 (26%)	158 (10%)	3.71 (2.74–5.02)	<0.001
Any biologic [¶]	14 (4%)	36 (2%)	2.47 (1.29–4.73)	0.006
Combined immunomodulator and biologic	22 (6%)	23 (1%)	5.85 (3.2–10.8)	<0.001
Persistent Use (> 365 days)	Cases (n=228)	Controls (n=913)	OR (95% CI) [^]	p value
None	154 (68%)	817 (89%)	1.0 (reference)	
Any immunomodulator**	56 (25%)	73 (8%)	4.45 (2.94–6.75)	<0.001
Any biologic [¶]	7 (3%)	13 (1%)	3.23 (1.24–8.45)	0.017
Combined immunomodulator and biologic	11 (5%)	10 (1%)	6.75 (2.74–16.65)	<0.001

* Only those with >365 days of exposure time prior to NMSC or index date were included in analyses of persistent medication use

[^] ORs and 95% CI by multiple variable conditional logistic regression adjusting for Medicaid insurance status

** Thiopurine class, calcineurin inhibitor, mycophenolate mofetil, methotrexate

[¶] Adalimumab or infliximab