Non-Melanoma Skin Cancer in Inflammatory Bowel Disease: A Review

Millie D. Long, MD, MPH[1], **Michael D. Kappelman, MD, MPH**[2], and **Clare A. Pipkin, MD**[3]

[1] University of North Carolina-Chapel Hill Department of Medicine, Division of Gastroenterology and Hepatology

[2] University of North Carolina-Chapel Hill Department of Pediatrics, Division of Gastroenterology and Hepatology

[3] Duke University, Department of Dermatology

Abstract

At least 1 million new cases of non-melanoma skin cancer (NMSC) are diagnosed in the United States each year, and the incidence is increasing. A higher incidence of non-melanoma skin cancer (NMSC) in organ transplant recipients on immunosuppression has been documented for some time, and recent studies indicate that patients with inflammatory bowel disease (IBD), particularly those treated with immunosuppressive medications, might also be at higher risk for this condition. In this review, we summarize recent data evaluating the associations between immunomodulators, anti-tumor necrosis factor-α (anti-TNF) biologic agents and NMSC in patients with IBD and other autoimmune conditions such as rheumatoid arthritis (RA). We also offer recommendations for prevention of NMSC in these populations.

Keywords

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

Introduction

Non-melanoma skin cancer (NMSC) is among the most common malignancies in the United States, especially among populations with lighter skin types. The annual incidence of NMSC had been estimated to be over 1,000,000 cases per year. A recent study has increased this estimate of the burden of NMSC to over 3.5 million annual cases, affecting over 2 million people (1). The causes of NMSC are multifactorial, including both environmental and host factors. Known environmental risk factors for NMSC include sun exposure (ultraviolet (UV) light), ionizing radiation, cigarette smoking, and certain chemical exposures such as arsenic. Host risk factors include human papilloma virus infection, genetic susceptibilities, skin type and immunosuppression (2). NMSC incidence increases with decreasing latitude, thereby demonstrating the increased risk associated with more intense sun exposure (3).

NMSC can be categorized into squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Both SCC and BCC occur more frequently on sunlight exposed areas such as the head and neck. BCC is far more common than SCC and accounts for approximately 75% of

Correspondence and Reprints: Millie D. Long MD, MPH, CB #7080, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7080, millie_long@med.unc.edu, Phone: 919-966-6000, Fax: 919-966-6842.

all NMSC (2). Treatment of NMSC consists of either excision, destruction, or use of topical immunomodulators. BCCs rarely metastasize to distant sites or lead to direct mortality and SCCs also carry a relatively low metastatic potential (less than one in twenty). However, those SCCs occurring at high risk areas, such as the lip, may have up to a 30% risk of metastasis (4). A previous review offered detailed information on diagnosis and treatment of NMSC (5).

Although the burden of NMSC measured in terms of mortality and morbidity is relatively modest, the direct costs of NMSC are quite substantial, owing to the high incidence. In fact, NMSC is more common than all other cancers combined. In the United States Medicare population, NMSC is among the 5 most costly cancers to treat (6). Additionally, NMSC has been associated with the development of other internal malignancies (7,8). For example, one study of internal malignancies following SCC of the skin found an increased risk of digestive tract malignancies (RR 1.6 95% CI 1.1–2.4)(8).

Patients with inflammatory bowel disease (IBD) may be at increased risk for NMSC due to the immunosuppressive medications used to treat the disease, the underlying immune dysfunction of IBD, or a combination of both factors. The increased risk of NMSC associated with solid organ transplant has been well described in the literature, and has been associated with both duration and level of immunosuppression (9–11). Until more recently, the risk of NMSC in patients on immunosuppression for the treatment of IBD has not been specifically quantified. As immunosuppressive medications and dosages used to treat IBD differ greatly from those used in the post-transplant setting, it is important to assess this risk in the IBD setting.

Incidence of NMSC in Patients with IBD

Three epidemiological studies have evaluated the risk of NMSC in the IBD population. In a recent retrospective cohort study of NMSC in patients with IBD, our group analyzed the procedural and outpatient pharmaceutical insurance claims in a sample of commercially insured individuals in the United States to determine the incidence of NMSC in patients with IBD compared to controls. Patients with IBD had a significantly increased risk of NMSC (IRR 1.64 95% CI 1.51–1.78). The overall annual incidence rate of NMSC for patients with IBD was 733 per 100,000, as compared to 447 per 100,000 for controls. Incidence rates for IBD patients and controls alike were increased in the South and the West, demonstrating the effects of latitude and sun exposure on NMSC risk (12).

Two other European studies have also shown an increased risk of NMSC in patients with IBD. In a Danish study, individuals with UC were found to have an increased risk of NMSC as compared to controls (RR 1.4, 95% CI 1.0–1.9)(13). However, this cohort of IBD patients was identified via hospital discharge records and may not be representative of the ambulatory IBD population. A second Swedish population-based cohort study found an increased risk of SCC in patients with IBD (SIR 2.2 95% CI 1.1–3.9), particularly CD (SIR 5.5 95% CI 2.0–11.9)(14). Both of these studies were performed in Northern European populations. Characteristics of this population including skin type, amount of sun exposure, and susceptibility to sun exposure may be different than that of patients with IBD in the United States. Table 1 summarizes the risks of NMSC in patients with IBD from these three studies. The risk estimate for SCC in the study by Ekbom et al was slightly higher than the estimates for NMSC in the other studies. These findings are mirrored in patients who have undergone solid-organ transplants, where the risk of SCC is increased to a greater extent than that of BCC (11). The two other studies of NMSC in IBD were not able to differentiate between SCC and BCC and only estimates for the combined outcome of NMSC are available. Despite inherent differences in the study design of each of these three

retrospective cohorts, the direction and magnitude of risk of NMSC are remarkably similar (Table 1).

Immunosuppression and NMSC: Epidemiological Studies of IBD

It has been suggested that the increased risk of NMSC in IBD patients might be related to the use of immunosuppressive medications (5). Indeed, several recent studies have begun to address this. Using a nested-case control design, our group studied the effects of different medication exposures on NMSC within an IBD population. Persistent (>365 days) use of the thiopurine class of medications in patients with IBD was associated with a markedly increased risk of NMSC (adjusted OR 4.27 95% CI 3.08–5.92) when compared to no immunosuppressive medication use, controlling for the use of other classes of immunosuppression. Persistent anti-TNF use among patients with CD was also associated with NMSC (adjusted OR 2.18 95% CI 1.07–4.46). Combined persistent use of thiopurines and anti-TNF agents in patients with CD appeared to confer the highest risk, adjusted OR 6.75 95% CI 2.74–16.65 (Table 2)(12). While this study could not attribute the increased risk of NMSC to specific durations of immunosuppression, length of therapy may be an important component of NMSC risk and warrants further investigation.

Immunosuppression and NMSC: Epidemiological Studies of RA

Additional evidence supporting an association between immunosuppressive use and NMSC comes from the RA literature. In the United States, an increased risk of NMSC in patients with RA compared to controls has been previously described (HR 1.19 95% CI 1.01–1.41) (15). However, these data should be interpreted with caution due to the small effect size and precision of the estimated increased risk. In patients with RA, studies have evaluated methotrexate and other non-biologic disease modifying antirheumatic drugs (DMARDs) and their associations with NMSC. Typical DMARDs used in the treatment of rheumatic disorders include: methotrexate, hydroxychloroquine, leflunomide, cyclosporine and less frequently: azathioprine. Chakravarty et al showed an increased risk of NMSC associated with prednisone (HR 1.28 95% CI 1.05–1.55), but not with methotrexate alone (HR 1.15 95% CI 0.81–1.64). There was also no increased risk of NMSC with leflunomide, which is not used in the treatment of IBD.

Biologic anti-TNF agents used in RA, alone or in combination with other DMARDs, have also been studied in association with NMSC. In a United States study of RA patients compared to control patients with osteoarthritis, there was no significant increased risk of NMSC with anti-TNF agents alone, although the point estimate was >1 (HR 1.24 95% CI 0.97–1.58). Combination therapy with methotrexate and anti-TNF agents was associated with significantly higher risk of NMSC (HR 1.97 95% CI 1.51–2.58)(15). Two recent papers presented at the 2009 American College of Rheumatology meeting also described the risk of NMSC in patients with RA treated with anti-TNF agents. In a study from the Department of Veterans' Affairs (VA) of 16,829 patients with RA, the effects of specific medications on NMSC risk were determined. The incidence of NMSC was 25.9 per 1000 patient-years in patients on anti-TNF agents, and 19.6 per 1000 patient-years in those on non-biologic DMARDs. Patients on anti-TNF agents had a higher risk of developing NMSC than those on non-biologic DMARDs (HR 1.34 95% CI 1.15–1.58). The increased risk of NMSC was a class effect and was not associated with specific anti-TNF agents (16). The second study used data from the BSR Biologics Register (BSRBR) and followed 11,757 consecutive patients with RA treated with anti-TNF agents. They were compared to 3515 biologic-naïve subjects receiving typical DMARDs. NMSC outcomes were obtained via record linkage to the United Kingdom national register for cancer. The incidence of NMSC among anti-TNF treated patients was 4.2 per 1000 patient-years versus 5.1 per 1000 patient years in patients

on DMARDs. The majority (90%) of the NMSC were BCCs. This finding is interesting, as the post-transplant literature has found an abundance of SCC in patients on other forms of immunosuppression for solid-organ transplant (17).

Possible Mechanisms of NMSC in IBD

The development of NMSC has been associated with exposure to sunlight and a diminished capacity to repair damaged DNA. Most NMSC occurs later in life, consistent with the estimated age-related decline in DNA repair capacity of 0.61% per year. Patients with increased sunlight exposure and reduced DNA repair capacity have a 5 fold greater risk of BCC (18).

To generate mechanistic hypotheses as well as to develop preventive strategies, an understanding of ultraviolet light (UV) is necessary. The sun emits UV radiation as part of an electromagnetic spectrum. The radiation is divided up into ultraviolet C (UVC) (200–280 nm), ultraviolet B (UVB) (280–320 nm) and ultraviolet A (UVA) (320–400 nm). UVC is almost completely absorbed by the atmosphere, and hence is not thought to be associated with any increase in skin cancer risk. In contrast, UVB is only partially absorbed by the atmosphere. UVB is the major spectrum which causes sunburn. Because of this, topical sunscreens were initially developed to block these rays (i.e. the sun protection factor (SPF) in sunscreens corresponds to UVB blockage). UVB causes direct damage to DNA due to the aromatic ring structures found in DNA. This injury leads to the formation of cyclobutane pyrimidine dimers. However, the majority of light that reaches the earth's surface is UVA light. UVA light can penetrate through glass and is present throughout the entire year. Patients may therefore be exposed to this harmful radiation inadvertently (19). In contrast to UVB, UVA is not absorbed by DNA but causes DNA damage and gentotoxic effects by indirect mechanisms. Generation of reactive oxygen species (ROS) and ROS-dependent DNA damage, including guanine oxidation, appear to be of particular importance for UVA-mediated mutagenesis (20). It is important to note that traditional sunscreens block only UVB, not UVA light.

Specific mechanisms of development of NMSC associated with the thiopurine class of immunosuppressive medications have also been proposed. O'Donovan et al. demonstrated that treatment with thiopurines causes 6-thioguanine (6-TG) to be incorporated into the DNA of skin. This results in selective UVA photosensitivity leading to a cascade of potentially harmful reactions. As previously mentioned, normal DNA does not absorb significant amounts of UVA wavelengths. However, azathioprine can act as a pro-drug of thioguanine nucleotides, causing an accumulation of 6-TG in cellular DNA. 6-TG has an absorption peak at 342 nm, within the UVA spectrum. When these cells are exposed to low levels of UVA radiation, the 6-TG metabolite is converted into two reactive oxygen species and guanine-6-sulfonate (G-6-SO$_3$) (which is also mutagenic). The resultant oxidative stress produces DNA lesions (19,21). The combination of UVA radiation and cell culture with 6-TG can also increase the number of mutations in a reporter gene. Therefore, thiopurines (via 6-TG metabolites) effectively increase the photosensitization of human skin (21). O'Donovan substantiated these findings by demonstrating a reduced minimal erythema dose (lowest amount of radiation required to produce erythema 24 hours after irradiation, a surrogate marker of persistent DNA damage) for UVA light in patients treated with azathioprine (21).

The specific mechanisms that mediate the risk of NMSC conferred by other immunosuppressive medications, including anti-TNF agents, are currently unknown. The cytokine TNF-alpha is a major mediator of inflammation. However, TNF also has actions of both tissue destruction and recovery from damage. In animal models, TNF is important in the destruction of tumor cells, via natural killer cells and CD8 lymphoctyes (22). TNF has

been associated with both selective destruction of tumor blood vessels and tumor promotion via contribution to the tissue remodeling and stromal development necessary for tumor spread (23). This dual nature of TNF may be one reason for the efficacy in reduction of inflammation and the potential for increased risk of NMSC as well as other malignancies associated with anti-TNF agents.

Immunosuppression in general may also exacerbate other recognized risk factors for malignancy. It has also been suggested that human papilloma virus (HPV) may be an important co-factor in the risk of NMSC, specifically in the development of SCC. At the higher levels of immunosuppression seen in post-transplant populations, SCC is the most common skin malignancy (9–11). Although cutaneous HPV types have relatively weak transforming activity in general, this is increased in the setting of immunosuppression and other risk factors such as sun exposure (24). Up to 90% of SCC lesions in immunosuppressed patients contain viral DNA. Furthermore, the HPV load in SCC lesions occurring in immunosuppressed patients is generally higher than that in lesions occurring in the general population. Therefore, although treatment with IBD generally requires a lower level of immunosuppression that that required for organ transplant recipients, it is possible that low levels of immunosuppression increase skin cancer risk independent of UV exposure.

Primary and Secondary Prevention of NMSC

Given the apparent increase in NMSC incidence, preventive strategies for NMSC are critical. Primary and secondary prevention can decrease the burden of NMSC in IBD patients. Although IBD-specific, evidence based guidelines for NMSC prevention do not exist as of 2010, the current recommendations for prevention of skin cancer for the general population may be particularly important in patients with IBD (25). Primary prevention via sun avoidance, sun protection or minimization of modifiable risk factors for NMSC should be recommended (26).

Sun protection strategies include protective clothing, hats, sunglasses and sunscreens. The Skin Cancer Foundation endorses clothing with a UPF (Ultraviolet Protection Factor; which measures the amount of UV that penetrates a fabric) of 30 or greater (27). Broad-spectrum sunscreens (UVA and UVB) with a SPF (sun protection factor, a measure of a sunscreen's ability to prevent erythema when the skin is exposed to solar radiation) of 30 or greater are recommended with regular reapplication. Patients often under apply the sunscreens or fail to reapply after two hours, leading to an actual SPF that is far lower than the stated SPF (26). The development of sunburn is primarily caused by UVB injury (28). UVA is involved in photoaging and contributes to skin carcinogenesis. Given the postulated mechanisms by which thiopurines may contribute to NMSC risk described above, minimizing UVA exposure might be of particular benefit in the IBD population who require these medications. In 2007, the federal drug administration (FDA) proposed a rating system for UVA filters, but this has not yet been approved for clinical use. At this point in time, patients can only select a product that claims broad-spectrum coverage. Additional radiation exposures such as tanning beds should be actively discouraged.

Novel strategies for counteracting the harmful effects of UV damage also include the use of antioxidants. When the buildup of ROS generated by UV and environmental stressors exhausts the body's innate defense mechanism of enzymatic and nonenzymatic antioxidants, damage to DNA can occur (26). Supplemental antioxidants can be used to help boost the neutralizing mechanisms. Antioxidants which have shown benefit in human studies include ferulic acid, polypodium leucotomos extract, vitamin C, vitamin E and green tea polyphenols (26).

Secondary prevention of NMSC in the form of appropriate skin screening for at-risk patients should also be considered. In the general population, the United States Preventive Services Task Force (USPSTF) determined that there is insufficient evidence to assess the balance of benefits and harms of screening for skin cancer by primary care clinicians or by patient self-skin examination (22). The critical gap in the evidence was the lack of data that early detection of skin cancer reduces mortality or morbidity. The balance of benefits and harms may be different in the IBD population, especially those on immunosuppressive medications. Any skin lesion suspicious for malignancy in a patient with IBD on immunosuppression should be evaluated by a trained dermatologist. Among solid-organ transplant recipients, annual skin examination is recommended by various transplant organizations (29–31). There are no guidelines for skin cancer screening in patients with IBD, as it is unclear whether the risk-benefit ratio of skin cancer screening in IBD patients correlates with that of the general population, or more closely with that of the solid organ transplant population. Consideration could be given in the future to skin cancer screening programs for patients with IBD on immunosuppression.

Conclusion

There is an increased risk of NMSC in patients with IBD compared to the general population. This risk is associated with particular classes of immunosuppression used in the treatment of IBD and other autoimmune conditions. Patients should be educated about this increased risk of NMSC at the initiation of immunosuppression, and counseled on sun protection strategies. As of yet, there are no guidelines for skin cancer screening in IBD patients.

Acknowledgments

Abbreviations

NMSC	non-melanoma skin cancer
BCC	basal cell carcinoma
SCC	squamous cell carcinoma
anti-TNF	anti-tumor-necrosis factor-α
IBD	inflammatory bowel disease
RA	rheumatoid arthritis
DMARDs	disease modifying antirheumatic drugs
UV	ultraviolet
6-TG	6 thioguanine
ROS	reactive oxygen species
HPV	human papilloma virus
UPF	universal protection factor
SPF	sun protection factor
USPSTF	United States Preventive Services Task Force

References

1. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States. Arch Dermatol. 2006; 146:283–287. [PubMed: 20231499]

2. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight. Adv Exp Med Biol. 2008; 624:89–103. [PubMed: 18348450]

3. Arora A, Attwood J. Common skin cancers and their precursors. Surg Clin North Am. 2009; 89:703–712. [PubMed: 19465206]

4. Ponten, F.; Lundeberg, J. Dermatology. 2. London: Harcourt Health Publishers Ltd; 2003. Principles of Tumor Biology and Pathogenesis of BCC's and SCC's; p. 1627-1639.

5. Maddox JS, Soltani K. Risk of nonmelanoma skin cancer with azathioprine use. Inflamm Bowel Dis. 2008; 14:1425–1431. [PubMed: 18383175]

6. Housman TS, Feldman SR, Williford PM, et al. Skin cancer is among the most costly of all cancers to treat for the Medicare population. J Am Acad Dermatol. 2003; 48:425–429. [PubMed: 12637924]

7. Friedman GD, Tekawa IS. Association of basal cell skin cancers with other cancers (United States). Cancer Causes Control. 2000; 11:891–897. [PubMed: 11142523]

8. Efird JT, Friedman GD, Habel L, et al. Risk of subsequent cancer following invasive or in situ squamous cell skin cancer. Ann Epidemiol. 2002; 12:469–475. [PubMed: 12377424]

9. Lindelof B, Sigurgeirsson B, Gabel H, et al. Incidence of skin cancer in 5356 patients following organ transplantation. Br J Dermatol. 2000; 143:513–519. [PubMed: 10971322]

10. Jensen P, Hansen S, Moller B, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol. 1999; 40:177–186. [PubMed: 10025742]

11. Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. N Engl J Med. 2003; 348:1681–1691. [PubMed: 12711744]

12. Long MD, Herfarth HH, Pipkin C, et al. Increased Risk for Non-Melanoma Skin Cancer in Patients with Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2009; 8(3):268–74. [PubMed: 20005977]

13. Mellemkjaer L, Olsen JH, Frisch M, et al. Cancer in patients with ulcerative colitis. Int J Cancer. 1995; 60:330–333. [PubMed: 7829239]

14. Ekbom A, Helmick C, Zack M, et al. Extracolonic malignancies in inflammatory bowel disease. Cancer. 1991; 67:2015–2019. [PubMed: 2004319]

15. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol. 2005; 32:2130–2135. [PubMed: 16265690]

16. Amari W, Zeringue AL, McDonald JR, et al. Non-Melanoma and Melanoma Skin Cancer Risk in a National Cohort of Veterans with Rheumatoid Arthritis [abstract]. Arthritis Rheum. 2009; 60 (Suppl 10):1379.

17. Mercer LK, Galloway JB, Lunt M, et al. The Influence of Anti-TNF Therapy Upon Incidence of Non-Melanoma Skin Cancer (NMSC) in Patients with Rheumatoid Arthritis (RA): Results From the BSR Biologics Register (BSRBR) [abstract]. Arthritis Rheum. 2009; 60 (Suppl 10):2062.

18. Wei Q, Matanoski GM, Farmer ER, et al. DNA repair and aging in basal cell carcinoma: a molecular epidemiology study. Proc Natl Acad Sci U S A. 1993; 90:1614–1618. [PubMed: 8434025]

19. Parrish JA. Immunosuppression, skin cancer, and ultraviolet A radiation. N Engl J Med. 2005; 353:2712–2713. [PubMed: 16371639]

20. Rodust PM, Stockfleth E, Ulrich C, et al. UV-induced squamous cell carcinoma--a role for antiapoptotic signalling pathways. Br J Dermatol. 2009; 161 (Suppl 3):107–115. [PubMed: 19775366]

21. O'Donovan P, Perrett CM, Zhang X, et al. Azathioprine and UVA light generate mutagenic oxidative DNA damage. Science. 2005; 309:1871–1874. [PubMed: 16166520]

22. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. Jama. 2006; 295:2275–2285. [PubMed: 16705109]

23. Balkwill F. Tumor necrosis factor or tumor promoting factor? Cytokine Growth Factor Rev. 2002; 13:135–141. [PubMed: 11900989]

24. Hengge UR. Role of viruses in the development of squamous cell cancer and melanoma. Adv Exp Med Biol. 2008; 624:179–186. [PubMed: 18348456]

25. Screening for skin cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009; 150:188–193. [PubMed: 19189908]

26. Wang SQ, Balagula Y, Osterwalder U. Photoprotection: a review of the current and future technologies. Dermatol Ther. 23:31–47. [PubMed: 20136907]

27. [Accessed 1 Apr 2010]. Available at: http://www.skincancer.org

28. Bolognia, JL.; Jorizzo, JL.; Rapini, RP., et al. Dermatology. 2. London: Elsevier; 2008.

29. Hofbauer GF, Anliker M, Arnold A, et al. Swiss clinical practice guidelines for skin cancer in organ transplant recipients. Swiss Med Wkly. 2009; 139:407–415. [PubMed: 19680830]

30. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV. 6.2. Cancer risk after renal transplantation. Skin cancers: Prevention and treatment. Nephrol Dial Transplant. 17(Suppl 4):31–36.

31. Kasiske BL, Vazquez MA, Harmon WE, et al. Recommendations for the outpatient surveillance of renal transplant recipients. American Society of Transplantation. J Am Soc Nephrol. 2000; 11(Suppl 15):S1–S86. [PubMed: 11044969]

Table 1

Risks of NMSC in Patients with Inflammatory Bowel Disease

Study	Cohort Location	IBD Population (n)	Skin Cancer Outcome	Risk Estimate vs. General Population	95% Confidence Interval
Ekbom et al, 1991	Sweden	IBD (4776)	SCC	SIR 2.2	1.1–3.9
Mellemkjaer et al, 1995	Denmark	UC (5546)	NMSC	RR 1.4	1.0–1.9
Long et al, 2010	US	IBD (53377)	NMSC	IRR 1.6	1.5–1.8

Table 2

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

Reproduced with permission from Clinical Gastroenterology and Hepatology12