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Risk of non-melanoma skin cancer in patients with a history of NMSC with the use of immunosuppressant and biologic agents in autoimmune disease

Frank I Scott, MD, MSCE[1,*], **Ronac Mamtani, MD, MSCE**[1,2,*], **Colleen M Brensinger, MS**[1,3], **Kevin Haynes, PharmD, MSCE**[1], **Zelma C Chiesa-Fuxench, MD**[4], **Jie Zhang, PhD**[5], **Lang Chen, PhD**[6], **Fenglong Xie, MS**[6], **Huifeng Yun, PhD**[5], **Mark T. Osterman, MD, MSCE**[1], **Timothy Beukelman, MD, MSCE**[5], **David J. Margolis, MD, PhD**[1,4], **Jeffrey R Curtis, MD, MS, MPH**[5,6,*], and **James D Lewis, MD, MSCE**[1,*]

[1]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania

[2]Abramson Cancer Center, University of Pennsylvania

[3]Department of Biostatistics and Epidemiology, University of Pennsylvania

[4]Department of Dermatology, University of Pennsylvania

[5]Department of Epidemiology, University of Alabama at Birmingham

[6]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham

Abstract

Importance—Immune dysfunction underlies the pathogenesis of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). Immunosuppressive therapy is the standard of care for these diseases. Both immune dysfunction and therapy-related immunosuppression can inhibit cancer-related immune surveillance in this population. Drug-induced immunosuppression is a risk factor for non-melanoma skin cancer (NMSC), particularly squamous cell tumors. For patients with a history of NMSC, data are limited on the impact of these drugs on the risk of additional NMSCs.

Corresponding Author: Frank I Scott, MD, MSCE, 3400 Civic Center Boulevard, 7th floor SPE, Philadelphia, PA 19104, frank.scott@uphs.upenn.edu; Telephone: 215 – 349 – 8222.

*Drs. Mamtani and Scott contributed equally to this work. Drs. Lewis and Curtis served as co-senior investigators.

Author Contributions: Drs James D. Lewis and Jeffrey Curtis had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Scott, Mamtani, Lewis, Curtis. Acquisition, analysis, and interpretation of data: Scott, Mamtani, Lewis, Curtis, Brensinger, Beukelman. Drafting of the manuscript: Scott, Mamtani. Critical revision of the manuscript for important intellectual content: Scott, Mamtani, Haynes, Chiesa-Fuxench, Chen, Xie, Yun, Osterman, Margolis, Brensinger, Lewis, Curtis. Statistical analysis: Brensinger, Lewis. Obtained funding: Lewis, Curtis, Scott, Mamtani. Administrative, technical, or material support: Brensinger, Lewis, Curtis. Study supervision: Lewis, Curtis.

Conflicts of interest/Disclosures

Dr. Lewis has served as a consultant for Takeda, Amgen, Millennium Pharmaceuticals, Prometheus, Lilly, Shire, AstraZeneca, Janssen Pharmaceuticals, Merck, and AbbVie. He has served on a Data and Safety Monitoring Board for clinical trials sponsored by Pfizer. He has received research support from Bayer, Shire, Centocor, Nestle, and Takeda. Dr. Curtis has served as a consultant for Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo and AbbVie. He has received research support from Roche/Genentech, UCB, Janssen, CORRONA, Amgen, Pfizer, BMS, Crescendo, and AbbVie. Dr. Beukelman has served as a consultant for Genentech, Novartis, and UCB. He has received research support from Pfizer. Dr. Zhang has received research support from Amgen. Dr. Osterman has served as a consultant for Janssen, Abbott, and UCB. He has received research support from UCB. Dr. Haynes has received research support from AstraZeneca/BristolMeyersSquibb. Dr. Mamtani has served as a consultant for Takeda. Drs. Scott, Brensinger, Chiesa-Fuxench, Chen, Xie, Yun, and Margolis report no potential conflicts of interest.

Objective—To determine the relative hazard of a second NMSC in RA or IBD patients who use methotrexate, anti-tumor necrosis factor (anti-TNF) therapy, or thiopurines after an initial NMSC.

Design—Retrospective cohort study.

Setting—Individuals enrolled in Medicare.

Participants—Individuals with RA or IBD from 2006–2012.

Exposure—Exposure to methotrexate, thiopurines, anti-TNFs, sulfasalazine, hydroxychloroquine, abatacept, or rituximab after the incident NMSC surgery.

Outcome—A second NMSC occurring ≥1 year after the incident NMSC, using Cox regression models.

Results—Among 9,460 individuals (6,841 with RA, 2,788 with IBD), the incidence rate of second NMSC per 1,000 person-years was 58.2 (95% CI, 54.5–62.1) and 58.9 (53.2–65.2) in RA and IBD, respectively. Among RA patients, methotrexate used in conjunction with other medications was associated with an increased risk of second NMSC (HR 1.60, 95% CI 1.08–2.37). Adjusted for other medications, the risk of NMSC increased with >1 year of methotrexate use (HR 1.24, 95% CI 1.04–1.48). Compared to methotrexate alone, the addition of anti-TNF drugs was significantly associated with risk of NMSC (HR 1.49, 95% CI 1.03–2.16). Abatacept and rituximab were not associated with increased NMSC risk. The HRs for >1 year of thiopurine and anti-TNF use for IBD were 1.49 (95% CI 0.98–2.27) and 1.36 (95% CI 0.76–2.44), respectively.

Conclusion—Methotrexate use is associated with an increased risk of second NMSC. Anti-TNF use may increase the risk of second NMSC when used with methotrexate for RA. Whether thiopurine and/or anti-TNF use in IBD increases the risk of second NMSC is uncertain; further long term studies are required before one can conclude that these immunosuppressive therapies do not increase the risk of second NMSC.

Introduction

The incidence of non-melanoma skin cancer (NMSC) is increasing in Caucasian populations worldwide[1]. Dermatologists, rheumatologists, gastroenterologists, and primary care physicians are capable of recognizing NMSC lesions, with most being treated by dermatologists[2]. Although initial surgical treatment is usually curative, the risk of second primary NMSC is high[3]. Major risk factors for NMSC are skin pigmentation and solar damage to the skin[4]. Medications that accelerate the phototoxic process have been associated with an increased incidence of NMSC[5]. Several medications are considered, “photosensitizers”, including methotrexate and thiopurines [6, 7]. This effect has not been reported with biologic therapies. Immunosuppression is also believed to be a risk factor for NMSC, particularly squamous cell carcinoma; this has prompted frequent screening of individuals after solid organ transplantation[8].

Immune dysfunction underlies the pathogenesis of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). Immunosuppressive therapies have become the standard for treating these diseases[9, 10]. Methotrexate was one of the first therapies with demonstrated benefit in RA, and has remained a cornerstone therapy[11]. Similarly, in IBD, thiopurine has

increased dramatically in recent decades[12]. These therapies have been further augmented by medications targeting tumor necrosis factor–alpha (anti-TNFs) and other targets, collectively referred to as biologic therapies[13, 14]. These agents are used alone or in combination with methotrexate or thiopurines[15–20].

Methotrexate, thiopurines, and anti-TNFs have been associated with hematologic and dermatologic malignancies[21–23]. Thiopurines appear to increase the risk of NMSC both during active use of the drug and possibly after the medication is discontinued[24, 25]. Similar effects were appreciated with methotrexate in a systematic review assessing the risk of NMSC in patients with psoriasis[26, 27]. The association between anti-TNFs and NMSC is less clear, with conflicting results among several studies [22, 27, 28].

For patients with a prior malignancy, there are limited data regarding the impact of these medications on the risk of cancer recurrence or a second primary. The available data are generally in small cohorts and have combined different cancer types[29–31]. In this study, we assessed the risk of a second NMSC in Medicare beneficiaries with RA or IBD exposed to methotrexate, thiopurines, or biologics. We hypothesized an increased risk for a second NMSC among patients with exposure to photosensitizers such as methotrexate or thiopurines relative to those who have received agents without these effects, such as anti-TNFs or non-immunosuppressive therapies.

Patients and Methods

We performed a retrospective cohort study among subjects with RA or IBD using Medicare data from 2006–2012. This cohort has been used previously to evaluate the comparative effectiveness and safety of medications used to treat IBD and RA[28, 32–34].

Inclusion criteria

Individuals aged ≥18 years with a diagnosis of RA or IBD based upon ICD-9 diagnosis codes, and an incident NMSC diagnosis after enrollment within Medicare from 2006–2010, were considered eligible for this study. Follow-up time continued for this cohort until 12/31/2012. Incident diagnoses of NMSC were identified using an adapted claims-based algorithm[35], combining diagnostic codes for NMSC and dermatologic procedures (See supplemental materials).

Subjects were required to have a baseline observation period of 6 months before the first NMSC diagnosis to assess medication exposures prior to or at the time of NMSC diagnosis[36]. Additionally, subjects were required to have ≥12 months of follow-up time after the first NMSC diagnosis or procedure, without an additional NMSC diagnostic or procedure code from 6–12 months to maximize the likelihood that subsequent NMSC codes represented incident events instead of follow-up for a prevalent NMSC(Supplemental Figure 1). This allowed 1 year for the completion of therapy for the incident NMSC event before diagnosis of a second NMSC; similar methods have been employed using administrative data to capture recurrent and second malignancies[37].

Exclusion Criteria

Individuals were excluded if they had an NMSC diagnosis within the first 6 months of enrollment or diagnosis with any of the following conditions prior to the first NMSC diagnosis: any malignancy, psoriasis, organ transplant, HIV, xeroderma pigmentosa, or albinism.[38, 39] We excluded patients with any recorded use prior to the first NMSC diagnosis of medications thought to affect the risk of NMSC, such as tacrolimus, cyclosporin, imiquimod, or fluorouracil. Individuals enrolled in Medicare Part C (Managed Medicare) were excluded, as they may have incomplete drug and outcome data. Follow-up was censored if patients met any exclusion criteria after first NMSC diagnosis.

Exposure definition

The following medications were considered exposures of interest: 1) methotrexate, 2) thiopurines (azathioprine/ 6-mercaptopurine), 3) anti-TNFs (infliximab, adalimumab, certolizumab, golimumab, or etanercept), 4) leflunomide, 5) tocilizumab, 6) abatacept, 7) rituximab, and 8) sulfasalazine (SSA) or hydroxychloroquine (HCQ). Exposure was defined as ≥2 dispensings or infusions within 4 months of each other, with at least one dispensing or infusion after the incident NMSC surgery. Exposure was further divided into current and recent exposure, where recent exposure began 90 days after the expected end of each prescription or infusion dosing interval if the medication was not continued. In addition, time updating variables describing cumulative exposure were generated for each medication. We assessed the duration of exposure for methotrexate, anti-TNFs, and thiopurines, categorized as never exposed, <1 year, 1–2 years, 2–3 years, and >3 years.

Outcome

Follow-up began 1 year after the first NMSC surgery. Follow-up ended with the earliest of the following: 1) subsequent new NMSC diagnosis using the same criteria as described above, 2) death, 3) loss of medical or prescription benefits, or 4) end of data-collection.

Potential confounders

Potential confounders were assessed at the start of follow-up, including age (in deciles), sex, race/ethnicity, urban versus rural residence, Charlson comorbidity scores, and nursing home inhabitance. Latitude was assessed as a dichotomous covariate, above or below the median for this cohort. A history of actinic keratosis and the number of dermatologic visits in the 12-month period between NMSC diagnosis and start of follow-up were assessed. Exposure to the medications of interest prior to the initial NMSC was evaluated as a potential confounder using all available data prior to the start of follow-up. Cumulative corticosteroid exposure was assessed as a confounder as a time-varying covariate measured in prednisone-equivalent dosing and categorized as no exposure, <1.5g, and >1.5g.

Statistical Analysis

Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and Stata version 13.0 (StataCorp, College Station, TX). Analyses were performed separately for RA and IBD. Our data use agreement with the Center for Medicare and Medicaid Services precluded reporting results where <11 patients were exposed to a therapy or experienced the outcome.

Baseline covariates were assessed using χ^2 and Fisher's exact tests as appropriate. We computed separate disease-specific Cox regression models for each exposure contrast of interest, adjusted for covariates. Covariates were selected for final multivariable models if inclusion changed the HR for the primary exposure by ≥10%. We computed time-updating HRs of each exposure of interest, adjusting for potential confounders. Test for interaction between our exposures of interest and follow-up time was used to ensure that proportional hazard assumptions were not violated (data not shown).

Because methotrexate is commonly used in combination with other therapies (HCQ, SSA or anti-TNF), we assessed the risk of NMSC with methotrexate plus HCQ or SSA versus HCQ or SSA alone and methotrexate plus anti-TNF versus anti-TNF alone. These analyses were limited to patients with documented methotrexate use prior to the first NMSC diagnosis. We computed the pooled association of methotrexate versus no methotrexate with second NMSC using fixed effects meta-analysis[40, 41]. Similar analyses were conducted for thiopurines and anti-TNFs in the IBD cohort. The study protocol was approved by University of Alabama at Birmingham and University of Pennsylvania institutional review boards.

Results

There were 9,460 individuals within the cohort: 6,841 had RA and 2,788 had IBD (Figure 1). 1,291 individuals developed a second NMSC. The incidence rate per 1,000 person-years of second NMSC was 58.2 (95%CI, 54.5–62.1) and 58.9 (53.2–65.2) among patients with RA and IBD, respectively. For both IBD and RA, males were more likely to have a second NMSC compared to females (p=0.01 and p<0.001, respectively) (Table 1). The median latitude for the cohort was 37.5 degrees; This was not associated with increased risk of second NMSC in IBD or RA. There was a greater prevalence of a history of actinic keratosis in those with a second NMSC in both RA and IBD (p<0.001).

Risk of second NMSC with methotrexate use in RA

The median methotrexate exposure time after an initial NMSC in RA was 1.64 years (IQR: 1.15–2.31) and 2.61 years (IQR:1.80–3.80) among those with and without a second NMSC, respectively. Among SSA/HCQ users, there was an increased risk of second NMSC with methotrexate exposure, though this was not statistically significant (HR 1.81, 95%CI 0.94–3.52) (Table 2). Similarly, there was an increased but not statistically significant risk of second NMSC with methotrexate use in patients also treated with anti-TNFs (HR 1.50, 95%CI 0.92–2.44). Using meta-analytic methods to pool these groups, methotrexate exposure was associated with an increased risk of second NMSC (HR 1.60, 95%CI 1.08–2.37).

We evaluated the impact of duration of methotrexate therapy after incident NMSC, categorizing methotrexate exposure as never exposed, short-term exposure (<1 year), and exposure >1 year. We observed an increased risk of NMSC with increasing duration of exposure, particularly among those exposed for >1 year (HR 1.24, 95%CI 1.04–1.48) (Table 3). After adjusting for age, sex, other immunosuppressive therapies, and latitude, the risk of a second NMSC increased with longer methotrexate exposure (<1 year HR 1.10, 95%CI

0.84–1.44; 1–2 years HR 1.16, 95%CI 0.95–1.41; 2–3 years HR 1.36, 95%CI1.05–1.77; >3 years HR 1.59, 95%CI 1.09–2.32).

Risk of second NMSC with anti-TNF, rituximab, and abatacept use for RA

Among patients treated with methotrexate for RA, there was no significant increased risk with rituximab or abatacept use, although anti-TNF use was statistically significant when adjusted for anti-TNF use prior to the first NMSC (HR 1.49, 95%CI1.03–2.16) (Table 2). When stratified by exposure duration, short-term anti-TNF use was significantly associated with increased risk (<1 year HR 1.43, 95%CI 1.01–2.04), but longer use was not (Table 3, Supplemental Table 3). Risks attributable to leflunomide were not calculated due to limited numbers of events. Cumulative steroid exposure was not significantly associated with risk of second NMSC in RA (p=0.53).

Risk of second NMSC with thiopurine and anti-TNF use for IBD

Among patients with IBD, thiopurine use was not associated with increased risk of second NMSC when used in combination with anti-TNF versus anti-TNF monotherapy (HR 0.79, 95%CI 0.30–2.08) (Table 2). In comparisons of anti-TNF versus thiopurine monotherapy, thiopurines appeared to have a higher incidence rate of second NMSC, although this was not statistically significant. Longer duration of anti-TNF use was not associated with an increased risk of a second NMSC (Supplemental Table 3). The risk of a second NMSC was increased with short-term (HR 1.53, 95%CI 0.87–2.70) thiopurine therapy and was nearly statistically significantly increased with >1 year of thiopurine therapy (HR 1.49, 95%CI 0.98–2.27) (Table 4). When further stratified by duration of exposure, the degree of risk remained similar, though was not significant (2–3 years: HR 1.57, 95%CI 0.83–2.97; >3 years HR 1.49, 95%CI 0.60–3.73). Cumulative steroid exposure was not significantly associated with second NMSC in IBD (p=0.89).

Discussion

In this retrospective cohort study, we examined the impact of immunosuppressant therapies on the risk of a second NMSC in patients with RA and IBD. We hypothesized that immunosuppressant medications used to treat RA and IBD, particularly methotrexate and thiopurines which are photosensitizing, may increase the risk of a second NMSC [5]. Among individuals with RA, methotrexate and anti-TNF drugs were both associated with an increased risk of second NMSC diagnosis. A similar strength of association was seen for anti-TNFs among the IBD cohort although this was not statistically significant. Abatacept or rituximab in conjunction with methotrexate were not associated with a significantly increased risk for a second NMSC compared to methotrexate monotherapy, although the point estimates were similar to anti-TNF agents and sample sizes were small. Therefore, one cannot interpret these results as demonstrating that these agents are safer alternatives. Among individuals with IBD, thiopurine use approached statistical significance for the association with an increased risk of second NMSC and the estimated relative risk was similar to that seen for methotrexate in RA.

For patients with RA, the incidence of second NMSC was increased by 19 per 1000 person-years when methotrexate was used with anti-TNFs and by 34 per 1000 person-years when methotrexate was used in addition to non-immunosuppressive therapies. This translates to a number needed to treat to cause one additional NMSC per year of 52.6 and 29.4 when used with anti-TNFs or without concomitant immunosuppressant medications, respectively. Given that methotrexate is generally the first line therapy for RA, with other drugs typically added to methotrexate when needed, these data emphasize the need for intensive NMSC surveillance protocols.

The evidence of an increased risk of a second NMSC among those treated with thiopurines for IBD was nearly statistically significant and consistent with several prior studies showing that thiopurines increase the incidence of a first NMSC. This failure to achieve statistical significance may have been due to inadequate statistical power, or may reflect a persistent effect of prior thiopurine exposure which would be expected among many of the anti-TNF treated patients in this cohort[24]. Likewise, if both thiopurines and anti-TNFs increase the risk of second NMSC, the association would be attenuated in direct comparisons of these two drug classes.

Anti-TNF therapy was significantly associated with the risk of second NMSC among patients with RA and the magnitude of risk was comparable in IBD. Prior studies in IBD have suggested an increased risk of melanoma with anti-TNF therapy, but there is less evidence for an increased NMSC [22, 27, 28]. In RA, the association between an initial NMSC and anti-TNFs appears more firmly established, though the relationship is often complicated by concomitant methotrexate use[42–46]. One can hypothesize that immunosuppression from anti-TNFs might contribute to NMSC risk, particularly in patients with a prior NMSC. In contrast to thiopurines and methotrexate, anti-TNF therapy is not photosensitizing. Regardless, these data suggest that anti-TNF therapy may not be an advantageous option over thiopurines or methotrexate for patients with a prior NMSC history.

This study has several important strengths. NMSC is the most frequently diagnosed malignancy in the United States[47]. Therefore, the risk of recurrence is an important question commonly faced in clinical practice, and research examining this risk has been limited to case reports and series[29–31]. This is by far the largest study to date examining the impact of commonly used therapies in IBD and RA on the risk of cancer recurrence. Furthermore, Medicare is a geographically diverse patient population and should be generalizable to approximately 93% of older adults in the US[48].

There are several potential limitations of this study. As with any retrospective study using claims-based data, there is the risk of misclassification. However, requiring both diagnostic and procedural codes to define NMSCs minimizes the probability of including individuals without a first NMSC in the cohort by maximizing the positive predictive value of a true incident event. There is also the potential for surveillance bias, as individuals with a prior NMSC who receive methotrexate or anti-TNF drugs may be more frequently surveyed than individuals not receiving these medications. To account for this, we adjusted for dermatology visits in the first year after the first NMSC. We are unable to ensure that our diagnostic codes identified exclusively second NMSC events as opposed to the initial event.

However, we employed a 1-year window after the initial diagnosis to minimize this misclassification. While we were unable to specifically measure disease severity in RA or IBD, we used corticosteroid exposure as a surrogate and found no significant association with second NMSC in univariate analysis and only one model with evidence of confounding. Because we studied NMSC, we cannot generalize these results to the risk of recurrence of other cancers. Our analysis was restricted to a predominantly Caucasian population, although this is the population that is at greatest risk for NMSC. We were also unable to assess NMSC risk according to specific ethnicity or sunscreen utilization.

We had limited power to study some of the drugs of interest. There were too few patients exposed to leflunomide. Similarly, sample sizes were small for analysis of abatacept, tocilizumab, and rituximab. The estimated HR with rituximab was among the highest observed, and there was some evidence of greater risk with longer therapy, but the confidence intervals were wide. Because rituximab is recommended among the biologic therapies for use in patients with a prior history of cancer in the ACR 2012 guidelines[49], this estimate may be biased by confounding by indication. Likewise, we were also unable to assess the impact of new thiopurine use in those who were thiopurine-naïve prior to their initial NMSC event due to limited numbers. This may represent reluctance on the part of providers to initiate therapy with thiopurines in individuals who have a known NMSC. Therefore, while this study demonstrated an increased risk of second NMSC with methotrexate and possibly anti-TNF drugs, we cannot conclude that the other immunosuppressive therapies represent safer alternatives. Further research examining these agents is required.

In summary, the use of immunosuppressive therapy is known to be a risk factor for NMSC, most commonly squamous cell carcinoma. Physicians treating patients with RA and IBD commonly face the decision of what medications to use in patients with a history of NMSC. In this study, methotrexate use was associated with an increased risk of a second NMSC in RA, with increasing risk with longer duration of exposure. While there appears to be a strong relationship between thiopurine use and an initial NMSC in IBD, we did not observe a statistically significant increased risk for a second NMSC, although this may have been due to reduced statistical power as the estimated relative risk with thiopurines for IBD was larger than that observed with methotrexate for RA. Lastly, anti-TNF therapy may further increase the risk of second NMSC particularly when used in conjunction with methotrexate to treat RA. These data can be used to guide therapeutic decisions in patients with prior NMSC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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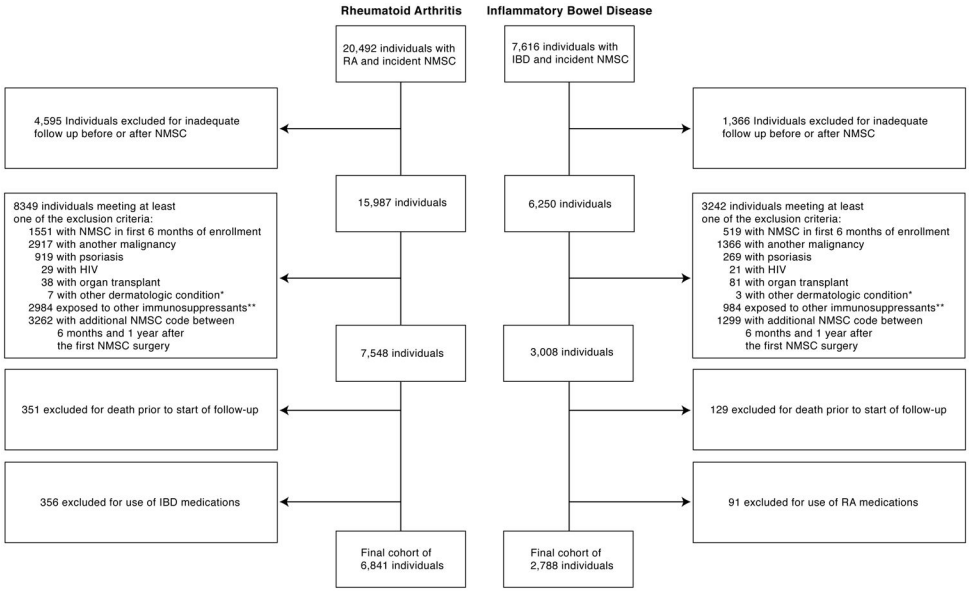

Figure 1.

Identification of cohort meeting inclusion and exclusion criteria.

Flowchart depicting identification of individuals meeting inclusion and exclusion criteria for study in both RA and IBD.

*Other dermatologic conditions consisted of xeroderma pigmentosa and albinism

** Other immunosuppressive therapies included tacrolimus, cyclosporin, imiquimod, or fluorouracil.

*** Cumulative exposure time is reported in Median (IQR), and is among those who had received the drug.

Table 1

Baseline Characteristics of individuals at cohort entry

		RA		IBD	
Characteristic	**Group**	**+ NMSC (n=932)**	**− NMSC (n=5909)**	**+ NMSC (n=381)**	**− NMSC (n=2407)**
Age	< 50	<10	63 (1.1%)	12 (3.1%)	48 (2.0%)
	51–60	23 (2.5%)	216 (3.7%)	<10	89 (3.7%)
	61–70	268 (28.8%)	1633 (27.6%)	113 (29.7%)	674 (28.0%)
	71–80	453 (48.6%)	2635 (44.6%)	179 (47.0%)	1035 (43.0%)
	81+	183 (19.6%)	1362 (23.0%)	73 (19.2%)	561 (23.3%)
Criteria for initial Medicare eligibility	Old Age and Survivors Insurance	757 (81.2%)	4609 (78.0%)	329 (86.4%)	2031 (84.4%)
	Disability and/or ESRD	175 (18.8%)	1300 (22.0%)	52 (13.6%)	376 (15.6%)
Sex	Female	582 (62.4%)	4310 (72.9%)	200 (52.5%)	1432 (59.5%)
	Male	350 (37.6%)	1599 (27.1%)	181 (47.5%)	975 (40.5%)
Race	White	925 (99.2%)	5802 (98.2%)	376 (98.7%)	2375 (98.7%)
	Black	<10	<10	<10	<10
	Other	<10	98 (1.7%)	<10	27 (1.1%)
Hispanic Ethnicity		<10	133 (2.3%)	<10	28 (1.2%)
Residence	Rural	280 (30.0%)	1861 (31.9%)	86 (22.6%)	584 (24.8%)
	Urban	652 (70.0%)	3981 (68.1%)	294 (77.4%)	1774 (75.2%)
Latitude (at or above median)	At or above median	445 (47.7%)	2948 (49.9%)	173 (45.5%)	1196 (49.7%)
	Below median	487 (52.3%)	2961(50.1%)	208(54.6%)	1211(50.3%)
Skilled nursing facility	Yes	43 (4.6%)	457 (7.7%)	18 (4.7%)	196 (8.1%)
Charlson co-morbidity score	0	413 (44.3%)	2527 (42.8%)	182 (47.8%)	1092 (45.4%)
	1	137 (14.7%)	930 (15.7%)	54 (14.2%)	345 (14.3%)
	2+	382 (41.0%)	2452 (41.5%)	145 (38.1%)	970 (40.3%)
Prior Anti-TNF		314 (33.7%)	2184 (37.0%)	43 (11.3%)	264 (11.0%)
Prior Methotrexate		815 (87.4%)	5005 (84.7%)	10 (2.6%)	96 (4.0%)
Prior Thiopurines		--	--	99 (26.0%)	529 (22.0%)
Prior Abatacept		35 (3.8%)	298 (5.0%)	--	--
Prior Rituximab		17 (1.8%)	152 (2.6%)	--	--
History of Actinic Keratotsis		615 (66.0%)	3128 (52.9%)	249 (65.4%)	1330 (55.3%)

Characteristic	Group	RA		IBD	
		+ NMSC (n=932)	− NMSC (n=5909)	+ NMSC (n=381)	− NMSC (n=2407)
Dermatology encounters in past year	Mean (SD)	1.7 (1.7)	1.4 (1.5)	1.8 (1.6)	1.6 (1.8)

Table 2

Risk of a second NMSC with immunosuppressive therapy in patients with Rheumatoid Arthritis and Inflammatory Bowel Disease

Combination of interest	Events	Person-years	Incidence rate (95% CI)	Adjusted HR (95% CI)
RA				
Methotrexate				
MTX with SSA/HCQ vs	72	913	78.9 (61.7–99.3)	1.81 (0.94–3.52)[a,b]
SSA/HCQ monotherapy	10	223	44.9 (21.5–82.6)	Ref
MTX with Anti-TNF vs	122	1,715	71.1 (59.08–84.94)	1.50(0.92–2.44)[a,b]
Anti-TNF monotherapy	19	367	51.8 (31.2–80.8)	Ref
Anti-TNF				
Anti-TNF with MTX vs	109	1,465	74.4 (61.1–89.8)	1.49 (1.03–2.16)[c]
MTX alone (ref)	335	4,631	72.3 (64.8–80.5)	Ref
Abatacept				
Abatacept with MTX vs		66	76.0 (24.7–177.4)	1.40 (0.48–4.03)[d]
MTX alone (ref)	319	4,311	74.0 (66.1–82.6)	Ref
Rituximab				
Rituximab with MTX vs		19	103.2 (12.5–373.0)	1.44 (0.26–8.08)[e]
MTX alone (ref)	320	4,301	74.4 (66.5–83.0)	Ref
IBD				
Thiopurine vs	63	717	87.9 (67.5–112.4)	1.23 (0.78–1.94)[f]
Anti-TNF (ref)	26	375	69.4 (45.3–101.6)	Ref
Anti-TNF with thiopurine vs		85	71.0 (26.0–154.5)	0.79 (0.30–2.08)[g]
anti-TNF monotherapy (ref)	26	351	74.0 (48.3–108.4)	Ref

[a] No covariates modified the HR by > 10%; covariates assessed included: anti-TNFs, SSA/HCQ, leflunomide, abatacept, rituximab, age, sex, median latitude, cumulative steroid exposure, and number of dermatology encounters in the year following surgery for the incident NMSC.

[b] Using meta-analytic methods to pool these two groups, methotrexate exposure was associated with an increased risk of second NMSC (HR 1.60, 95% CI 1.08–2.37)

[c] Adjusted for Anti-TNF exposure prior to the incident NMSC diagnosis, no other covariates modified the HR by > 10%;.

[d] Adjusted for abatacept exposure prior to the incident NMSC diagnosis, no other covariates modified the HR by > 10%;

[e] Adjusted for rituximab exposure prior to the incident NMSC diagnosis, no other covariates met the 10% change criteria for confounding.

[f] No covariates modified the HR by > 10%;.

[g] Adjusted for thiopurine exposure prior to the incident NMSC diagnosis, no other covariates modified the HR by > 10%.

Table 3

Cumulative duration of medication exposure on risk of second NMSC in Rheumatoid Arthritis

Drug	Never exposed	Recent exposure	Short-Term exposure (<1year)	Long-term exposure (>1year)
Methotrexate				
Events	271	54	85	499
Person-years	5,041	1,647	1,089	7,538
Incidence Rate per 1000 person-years	53.8 (47.5–60.5)	32.8 (24.6–42.8)	78.1 (62.4–96.5)	66.2 (60.5–72.3)
Adjusted HR[a]	Ref	0.81 (0.60–1.11)	1.12 (0.86–1.47)	1.24 (1.04–1.48)
Anti-TNF				
Events	662	32	39	176
Person-years	10,875	926	440	3,073
Incident Rate	60.9 (56.3–65.7)	34.6 (23.6–48.8)	88.5 (63.0–121.0)	57.3 (49.1–66.4)
Adjusted HR[a]	Ref	0.87 (0.59–1.29)	1.43 (1.01–2.04)	1.11 (0.87–1.42)
Abatacept				
Events	858	5	15	31
Person-time	14,397	212	205	500
Incident Rate	59.6 (55.7–63.7)	23.6 (7.6–55.0)	73.3 (41.0–120.9)	62.0 (42.1–88.0)
Adjusted HR[a]	Ref	0.72 (0.29–1.79)	1.48 (0.87–2.51)	1.51 (0.94–2.41)
Rituximab				
Events	890	6	5	8
Person-time	14,837	179	119	180
Incident Rate	60.0 (56.1–64.1)	33.6 (12.3–73.1)	41.8 (13.6–97.6)	44.6 (19.2–87.8)
Adjusted HR[a]	Ref	1.01 (0.44–2.35)	0.78 (0.32–1.92)	1.20 (0.55–2.61)

[a]Adjusted for use of anti-TNFs, SSA/HCQ, methotrexate, leflunomide, abatacept, rituximab, age, sex, median latitude, cumulative steroid exposure, and number of dermatology encounters in the year following surgery for the incident NMSC.

Table 4

Cumulative impact of medication exposure on risk of second NMSC in Inflammatory Bowel Disease

Drug	Never exposed	Recent exposure	Short-Term exposure (<1year)	Long-term exposure (>1year)
Anti-TNF				
Events	332	4	8	27
Person-time	5,635	116	84	424
Incidence rate per 1,000 person years	58.9 (52.7–65.6)	34.4 (9.4–88.2)	95.0 (41.0–187.9)	63.7 (42.0–92.8)
Adjusted HR[a]	Ref	0.95 (0.33–2.66)	1.34 (0.64–2.81)	1.36 (0.76–2.44)
Thiopurine				
Events	295	6	16	54
Person-time	5,240	189	132	697
Incidence rate per 1,000 person years	56.3 (50.1–63.1)	31.7 (11.6–69.0)	121.0 (69.2–196.5)	77.5 (58.2–101.1)
Adjusted HR[a]	Ref	0.70 (0.30–1.65)	1.53 (0.87–2.70)	1.49 (0.98–2.27)

[a]Adjusted for use of anti-TNFs and thiopurines, age, sex, median latitude, cumulative steroid exposure, and number of dermatology encounters in the year following surgery for the incident NMSC.