Risk of non-melanoma skin cancer in a national cohort of veterans with rheumatoid arthritis

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Abstract

Objective. To determine the incidence of and risk factors for non-melanoma skin cancer (NMSC) in a national cohort of veterans with RA.

Methods. We examined skin cancer risk in a cohort of 20,648 patients with RA derived from the Department of Veterans’ Affairs (VA) national administrative databases. The cohort was divided into two medication groups: patients treated with non-biologic and TNF-α antagonist DMARDs. We defined skin cancer as the first occurrence of an International Classification of Disease, Version 9, Clinical Modification (ICD-9-CM) code for NMSC after initiation of a DMARD. Outcome risk was described using hazard ratios (HRs) with Cox proportional hazards regression for time-to-event analysis and logistic regression. We performed medical record review to validate the diagnosis of NMSC.

Results. Incidence of NMSC was 18.9 and 12.7 per 1000 patient-years in patients on TNF-α antagonists and non-biologic DMARDs, respectively. Patients on TNF-α antagonists had a higher risk of developing NMSC (HR 1.42; 95% CI 1.24, 1.63). Risk factors for NMSC included older age, male gender, NSAID and glucocorticoid use and a history of prior malignancies. There was substantial agreement between ICD-9-CM diagnosis of NMSC and medical record validation (κ = 0.61).

Conclusion. TNF-α antagonist therapy in veterans with RA may be associated with an increased risk of NMSC, compared with therapy with non-biologic DMARDs. Rheumatologists should carefully screen patients receiving TNF-α antagonists for pre-cancerous skin lesions and skin cancer.

Key words: Non-melanoma skin cancer, Non-biologic, TNF antagonist, DMARDs, Rheumatoid arthritis.

Introduction

The introduction of the TNF-α antagonists in 1998 revolutionized the treatment of RA. Over the past decade, significant complications associated with the use of this class of drugs have emerged, including the risk of serious infections and malignancy. In March 2003, the Food and Drug Administration and its Arthritis Advisory Committee added a warning regarding the potential risk of malignancy to the labelling of TNF-α antagonists (www.fda.gov/medwatch/safety). Since then, numerous studies have examined the risk of cancer associated with these drugs [1-11]. Whether there is an increased risk of cancer overall with the use of this class of biologic agents remains controversial. Several studies have shown no increase in cancer risk [6, 8, 9, 11], whereas others have shown excess risk associated with TNF-α antagonist use [1, 10]. However, when cancers are considered individually, there appears to be a trend of increased skin cancer risk across studies [5, 7, 11].

Non-melanoma skin cancer (NMSC) is the most common cancer in the USA with more than one million new cases estimated yearly (www.skincancer.org, www.SEER.cancer.gov). Known risk factors for NMSC include older age, male gender, fair skin, ultraviolet (UV) light exposure, organ transplantation, haematological malignancies and glucocorticoid use [12-19]. NSAID use may be protective against the development of NMSC [20]. An enhanced
understanding of skin cancer risk associated with TNF-\(\alpha\) antagonist use is important because these drugs are being increasingly used in older individuals who may have risk factors for skin cancer.

In this study, we used the Veterans’ Affairs (VA) national administrative databases to evaluate the risk of NMSC in a national cohort of veterans with RA who received a DMARD for the first time. We hypothesized that treatment with TNF-\(\alpha\) antagonists is associated with an increased risk of skin cancer in RA patients.

Materials and methods

This study was approved by the institutional review boards of the participating institutions (the St Louis, Denver, Hines, Albany, Salt Lake City and Minneapolis VA Medical Centers).

Databases

We acquired data from the Austin Information Technology Center (AITC) and the pharmacy benefits management (PBM) databases, which contain the VA’s centralized national administrative data. AITC data included all inpatient and outpatient International Classification of Diseases, Version 9, Clinical Modification (ICD-9-CM) diagnosis codes, encounter data and demographic data. PBM data included all inpatient and outpatient pharmacy data. Data from both the AITC and PBM were merged into a single database.

Study sample

Veterans who met the following criteria between 1 October 1998 and 30 September 2008 were included in the study: (i) received an ICD-9-CM diagnosis code of RA (714.0, 714.1, 714.2 or 714.81); (ii) received at least one prescription for a DMARD from the VA; (iii) had at least a 4-month history of receiving medication from the VA before the first DMARD prescription; and (iv) had at least two separate clinic visits during the study period. Patients were excluded if they: (i) had a diagnosis of NMSC at any time before receiving their first DMARD; (ii) did not have age or gender recorded; or (iii) had missing or unknown race. Patient records were censored at the date of last DMARD prescription, the last clinical encounter or first diagnosis of NMSC, whichever occurred last. Uncensored patients were followed through 30 September 2008.

Definitions

RA

Based on an algorithm validated by Singh et al. [21], the diagnosis of RA required both: (i) the occurrence of an ICD-9-CM code for RA on at least one occasion in either the inpatient or outpatient record; and (ii) the receipt of a prescription for a DMARD on at least one occasion.

Medication group (DMARDs)

DMARDs were characterized as non-biologic DMARDs and TNF-\(\alpha\) antagonist DMARDs. The following drugs were defined as non-biologic DMARDs: HCQ, MTX, SSZ, LEF, AZA, CYC, cyclosporin, oral and injectable gold and penicillamine. TNF-\(\alpha\) antagonist DMARDs included etanercept, infliximab and adalimumab. Patient time on DMARD was assigned to one of these groups, but not both: patients receiving a TNF-\(\alpha\) antagonist were considered to be in the TNF-\(\alpha\) antagonist group, regardless of whether they were also receiving a non-biologic DMARD. In the TNF-\(\alpha\) antagonist DMARD group, time zero started with first TNF-\(\alpha\) antagonist prescription and ended with censorship or time of last prescription, whichever occurred first. In the non-biologic DMARD group, time zero started with first non-biologic DMARD first prescription and ended with censorship or time of last prescription, or with first receipt of a TNF-\(\alpha\) antagonist, whichever occurred first. Thus, a patient assigned to the non-biologic group could subsequently switch to the TNF-\(\alpha\) antagonist DMARD group, but not vice versa.

Glucocorticoids

Glucocorticoid use was a binary yes/no variable [15] defined as the use of the following for at least 1 consecutive month at some time during the study period: prednisone \(\geq 5\) mg/day, prednisolone \(\geq 5\) mg/day, methylprednisolone \(\geq 4\) mg/day, dexamethasone \(\geq 0.8\) mg/day, hydrocortisone \(\geq 20\) mg/day, cortisol \(\geq 25\) mg/day and triamcinolone \(\geq 4\) mg/day.

NSAIDs

NSAID use was a binary yes/no variable, defined as any non-selective NSAID or cyclo-oxygenase 2 (COX-2) selective inhibitor used for \(\geq 5\) years at some time during the study period.

NMSC

NMSC was defined by the following ICD-9-CM diagnosis codes: 173.0–173.9, 232. NMSC diagnosis was accepted if cancer developed anytime after patient’s first DMARD even if the DMARD had been discontinued for any reason.

Other covariate definitions

Available as supplementary data at Rheumatology Online.

Validation

The accuracy of ICD-9-CM diagnosis of NMSC was evaluated by medical record review by the principal investigator (W.A.). For convenience, validation was performed at the principal investigator’s affiliated medical centre. The medical records of all subjects at a single medical centre (St Louis VA Medical Center) with ICD-9-CM code for NMSC (71 subjects) were reviewed for the diagnosis of skin cancer. Medical records of 198 subjects without an NMSC code were selected for review using a random number generator. Each patient’s medical record accessed from the VA’s computerized patient record system (CPRS) was electronically queried using the CPRS search function for the following text strings: NMSC, squam, basal, squamous cell carcinoma, basal cell carcinoma and skin cancer. Text strings were identified based on a priori review of the medical records of 10 subjects with pathology-proven NMSC to examine how clinicians describe NMSC in the
clinical record. All notes containing these strings were reviewed in detail for diagnosis of NMSC. If clinicians used the words probable and likely in their notes, NMSC diagnosis was accepted, while possible and questionable diagnoses were rejected. In addition, pathology reports were reviewed for each patient for evidence of skin cancer by biopsy results. Diagnoses for basal and squamous cell carcinoma were accepted. Only diagnoses within 90 days of an ICD-9-CM code were accepted.

**Statistical analysis**

Cox proportional hazards regression was used to perform time-to-event analyses, including a primary model examining risk factors for NMSC and secondary models examining the relationship between TNF-α antagonist duration and skin cancer, differences in skin cancer risk between patients receiving TNF-α antagonists and those receiving MTX and differences in skin cancer risk between the three individual TNF-α antagonists. A two-sided $P < 0.05$ was considered statistically significant. Outcome risk was described using hazard ratios (HRs). Membership in medication group (TNF-α antagonist vs non-biologic DMARD and TNF-α antagonist vs MTX) was modelled as a time-dependent dummy variable to account for changes in the medication groups over time. Each medication group was modelled separately and adjusted for age, gender, race and comorbid diagnoses, which are known or putative risk factors for the outcomes of interest.

Covariates in the multivariate models were treated as time-dependent variables, and thus were associated with a medication group only if they occurred before or during their time in that medication group. In addition to these covariates, we adjusted for mean number of health-care encounters per month in all of our models. In order to minimize confounding by indication, we also included a propensity score modelling the likelihood of receiving a TNF-α antagonist to reflect the severity of RA in our multivariate models [22]. This was created using logistic regression, and the following variables were included: age, baseline Romano score [23], IA glucocorticoid injections and orthopaedic procedures. All analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC, USA). The time-to-event graphs were created using R software version 2.5.1 (R Foundation, Vienna, Austria).

**Results**

Demographics and clinical characteristics of RA cohort

Between October 1998 and September 2008, there were 20,648 patients with RA receiving their first DMARD prescription who met the inclusion criteria (Fig. 1). There were 18,396 patients who contributed patient time to the non-biologic DMARD cohort and 4088 patients who contributed patient time to the TNF-α antagonist cohort. Patient demographics, comorbidities and DMARD treatment are shown in Table 1. As expected from a VA database, >90% of our cohort was male. Over 50% of patients in both groups were on MTX. Among patients who received TNF-α antagonists, etanercept was the most frequently used agent, received by 68% of patients. The burden of solid tumours was high in both groups, including 20.0% of patients on TNF-α antagonists and 24.6% of patients on non-biologic DMARDs.

Validation of ICD-9-CM codes by medical record review

A medical record review to validate ICD-9-CM codes of NMSC showed that 43 out of 71 patients with an ICD-9-CM code for NMSC had this diagnosis within 90 days of receiving the code, for a positive predictive value of 60%. Of the 43 subjects who had valid diagnoses of NMSC, 38 were confirmed by pathology and only 5 required text string identification. A total of nine patients without a NMSC ICD-9-CM code had a diagnosis of NMSC validated by chart review, for a negative predictive value of 95%. Of these nine, two had been exposed to TNF-α antagonists during the study period and seven had not. The $\kappa$ statistic for agreement between the ICD-9-CM code diagnosis and the medical record diagnosis was 0.61, indicating substantial agreement.

Based on the results of the validation with a $\kappa$ statistic of 0.61, we addressed potential misclassification of our outcome variable (NMSC) by performing a sensitivity analysis. Using our existing data set and based on the results from our validation study, we created 100 new data sets. In each, subjects with an NMSC diagnosis code were randomly assigned with a 0.4 probability to no NMSC diagnosis. Conversely, subjects without an NMSC diagnosis code were randomly assigned with a 0.05 probability to a NMSC diagnosis. Subject time in cohort was not altered. For each data set, we performed an adjusted survival model, yielding 100 new estimates of TNF-α antagonist effect. For every model, TNF-α antagonist effect was significant ($P < 0.05$). The median HR was 1.32 (95% CI 1.21, 1.42).

Incidence and risk factors for NMSC

Patient time in the non-biologic DMARD group was 82,291 patient-years, and in the anti-TNF group was 11,084 patient-years. NMSC occurred at a rate of 18.9 per 1000 patient-years in the TNF-α antagonist cohort. In a multivariate model, including adjustment for mean number of health-care encounters per month and propensity to receive a TNF-α antagonist, patients diagnosed with NMSC were older, predominantly male and Caucasian (Table 2). Patients on TNF-α antagonists had a higher risk of developing NMSC compared with those on non-biologic DMARDs (HR 1.42; 95% CI 1.24, 1.63). Both NSAID and glucocorticoid use were independent risk factors for NMSC, as was a history of either a solid or a haematological malignancy. Patients on non-biologic DMARDs had a longer NMSC-free survival than patients on TNF-α antagonists ($P < 0.001$) (Fig. 2). In exploratory analyses, the mean number of health-care encounters per month was associated with risk of skin cancer independent of comorbid illnesses, possibly due to increased number of opportunities for detection of skin lesions by a health-care
Fig. 1 Study flow diagram. Inclusion criteria: ICD-9-CM code diagnosis of RA between 1 October 1998 and 30 September 2008, and who, after at least a 4-month history of receiving medications from the VA, subsequently received at least one prescription for a DMARD and had at least two separate outpatient or inpatient clinical encounters during the study period. The sum of subject numbers in two medication groups exceeds the total number in the primary cohort because of overlap between medication groups as subjects in the TNF-α antagonist group may have been on one or more non-biologic DMARDs before their entry into that group. Patient time was assigned to the TNF-α antagonist medication group if patient was receiving or had received etanercept, infliximab or adalimumab. Patient time was assigned to the non-biologic medication group if patient was receiving SSZ, HCQ, oral or injectable gold, penicillamine, MTX, AZA, LEF, CYC or ciclosporin and had never received a TNF-α antagonist.

Effect of TNF-α antagonist duration, MTX and individual TNF-α antagonists on skin cancer risk

Among patients who received TNF-α antagonists, the unadjusted incidence of NMSC was not influenced by the duration of TNF-α antagonist exposure (Fig. 3). In a separate multivariate model that included duration of TNF-α antagonist exposure, after adjusting for covariates, duration of TNF-α antagonist exposure was not associated with increased NMSC risk [odds ratio (OR) 0.99 per duration interval; 95% CI 0.98, 0.99]. Secondary multivariate analyses performed to evaluate the risk of NMSC in patients on MTX compared with TNF-α antagonists showed a higher risk of NMSC with the TNF-α antagonists (HR 1.42; 95% CI 1.23, 1.65) compared with MTX. When each of the three TNF-α antagonists was considered separately, we found that patients on adalimumab or infliximab had a higher risk of NMSC than those on etanercept, with the risk with adalimumab being significant ($P < 0.0001$) (Table 3).
### Table 1: Demographic and clinical characteristics of RA cohort

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Whole cohort</th>
<th>TNF-α antagonist cohort</th>
<th>Non-biologic cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of subjects</td>
<td>19,200</td>
<td>4,088</td>
<td>18,396</td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>62.9 (12.3)</td>
<td>59.6 (11.4)</td>
<td>63.1 (12.3)</td>
</tr>
<tr>
<td>Gender: males</td>
<td>17,421 (90.7)</td>
<td>3,687 (90.4)</td>
<td>16,767 (90.6)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, not Hispanic</td>
<td>15,366 (80.0)</td>
<td>3,307 (80.9)</td>
<td>14,669 (79.9)</td>
</tr>
<tr>
<td>Black</td>
<td>2519 (13.1)</td>
<td>461 (11.3)</td>
<td>2,451 (13.3)</td>
</tr>
<tr>
<td>Other</td>
<td>1,315 (6.9)</td>
<td>320 (7.8)</td>
<td>1,256 (6.8)</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>17,290 (90.1)</td>
<td>3,765 (92.1)</td>
<td>16,525 (90.3)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>11,582 (60.3)</td>
<td>2,757 (67.4)</td>
<td>10,825 (60.2)</td>
</tr>
<tr>
<td>Other glucocorticoids</td>
<td>670 (3.5)</td>
<td>157 (3.8)</td>
<td>513 (3.2)</td>
</tr>
<tr>
<td>MTX</td>
<td>10,990 (57.2)</td>
<td>2,230 (54.5)</td>
<td>10,760 (57.6)</td>
</tr>
<tr>
<td>LEF</td>
<td>3,014 (15.7)</td>
<td>906 (22.2)</td>
<td>2,108 (14.6)</td>
</tr>
<tr>
<td>HCQ</td>
<td>9,284 (48.4)</td>
<td>1,073 (26.2)</td>
<td>8,211 (48.8)</td>
</tr>
<tr>
<td>SSZ</td>
<td>5,520 (28.8)</td>
<td>801 (19.6)</td>
<td>4,719 (28.4)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>857 (4.5)</td>
<td>857 (21.0)</td>
<td>0.0</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1,695 (8.8)</td>
<td>1,695 (41.5)</td>
<td>0.0</td>
</tr>
<tr>
<td>Etanercept</td>
<td>2,782 (14.5)</td>
<td>2,782 (68.0)</td>
<td>0.0</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukaemia/lymphoma</td>
<td>512 (2.7)</td>
<td>61 (1.5)</td>
<td>470 (2.6)</td>
</tr>
<tr>
<td>Solid tumour</td>
<td>4,725 (24.6)</td>
<td>817 (20.0)</td>
<td>4,908 (23.7)</td>
</tr>
<tr>
<td>Obesity</td>
<td>5,363 (27.9)</td>
<td>1,315 (32.2)</td>
<td>4,048 (26.7)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>2,501 (13.0)</td>
<td>624 (15.3)</td>
<td>2,277 (12.3)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>5,617 (29.3)</td>
<td>1,401 (34.3)</td>
<td>4,216 (25.3)</td>
</tr>
<tr>
<td>Incidence (per 1000 patient-years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMSC</td>
<td>1,326 (6.9)</td>
<td>283 (6.9)</td>
<td>1,043 (6.9)</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) unless otherwise noted.

### Table 2: Multivariate risk factors for NMSC

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Patients with NMSC</th>
<th>Patients without NMSC</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total subjects (n)</td>
<td>1,326</td>
<td>17,874</td>
<td></td>
</tr>
<tr>
<td>Age by decade, mean (s.d.), years</td>
<td>66.6 (10.3)</td>
<td>62.6 (12.4)</td>
<td>1.23 (1.09, 1.38)</td>
</tr>
<tr>
<td>Gender: males</td>
<td>1,258 (94.9)</td>
<td>16,163 (90.4)</td>
<td>1.34 (1.05, 1.73)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1,257 (94.8)</td>
<td>1,410 (78.9)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>18 (1.4)</td>
<td>250 (14.0)</td>
<td>0.08 (0.05, 0.13)</td>
</tr>
<tr>
<td>Other</td>
<td>51 (3.9)</td>
<td>1,264 (7.1)</td>
<td>0.45 (0.34, 0.60)</td>
</tr>
<tr>
<td>NSAID use</td>
<td>1,217 (91.8)</td>
<td>16,056 (89.8)</td>
<td>1.28 (1.05, 1.57)</td>
</tr>
<tr>
<td>Glucocorticoid use</td>
<td>862 (65.0)</td>
<td>10,901 (61.0)</td>
<td>1.18 (1.05, 1.32)</td>
</tr>
<tr>
<td>TNF-α antagonist use</td>
<td>2,833 (21.3)</td>
<td>3,805 (21.3)</td>
<td>1.42 (1.24, 1.63)</td>
</tr>
<tr>
<td>Non-biologic DMARD use</td>
<td>1,043 (78.7)</td>
<td>14,069 (78.7)</td>
<td></td>
</tr>
<tr>
<td>Leukaemia/lymphoma</td>
<td>50 (3.8)</td>
<td>462 (2.6)</td>
<td>1.44 (1.08, 1.92)</td>
</tr>
<tr>
<td>Solid tumour</td>
<td>558 (42.1)</td>
<td>4,167 (23.3)</td>
<td>2.58 (2.30, 2.90)</td>
</tr>
<tr>
<td>Obesity</td>
<td>332 (25.0)</td>
<td>5,031 (28.2)</td>
<td>1.00 (0.88, 1.13)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>105 (7.9)</td>
<td>2,396 (13.4)</td>
<td>0.82 (0.67, 1.01)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>307 (23.2)</td>
<td>5,310 (29.7)</td>
<td>1.06 (0.93, 1.22)</td>
</tr>
</tbody>
</table>

Data are expressed as n (%) unless otherwise noted. Model includes adjustment for mean number of health-care encounters per month and propensity to receive TNF-α antagonist.  

*Reference category for race.  

*Reference category for TNF-α antagonist use.
Discussion

In a large observational cohort of RA patients derived from the VA’s national administrative databases, we established that the risk of NMSC in patients treated with TNF-α antagonists is higher than those treated with non-biologic DMARDs. Previous studies have reported an increased risk of NMSC in patients treated with TNF-α antagonists. In a RA registry with questionnaire-based follow-up, Chakravarty et al. [5] examined NMSC risk in 15,784 RA patients. Use of TNF-α antagonists alone showed a non-significant trend towards higher risk of NMSC, but TNF-α antagonists were significantly associated with NMSC when used in combination with MTX. In a follow-up study from the same registry, among 13,001 patients with RA, Wolfe and Michaud [11] observed an increased risk of NMSC [relative risk (RR) 1.5; 95% CI 1.2, 1.8; P < 0.001] associated with the use of TNF-α antagonists. In a population-based study using a Swedish cancer registry, Askling et al. [6] found increased risk of NMSC associated with TNF-α antagonists (RR 3.6; 95% CI 1.8, 6.5), but this finding was based on only 11 cases of NMSC in the TNF-α antagonist-treated population.

Our study differed from these studies in several important ways. Askling et al. [6] did not adjust for relevant skin cancer-specific covariates, and had very few episodes of NMSC among patients receiving TNF-α antagonists. Compared with the studies of Chakravarty and Wolfe, our outcomes were based on administrative codes instead of patient self-report, and our multivariate model included adjustment for several potentially significant covariates that their studies did not, including history of other cancers and mean number of health-care encounters per month. We compared the risk of skin cancer between the three individual TNF-α antagonists and found a significantly higher risk with adalimumab. Of note, a larger number of patients were on etanercept with greater exposure compared with adalimumab (n = 2782 vs 1695; patient-years 6827 vs 2583, respectively), but this was likely due to the fact that etanercept was approved for RA in 1998 and hence was in use longer than adalimumab that was approved in 2001. Despite these and other differences in methodology, our point estimate for NMSC risk associated with TNF-α antagonist use (1.42) was similar to those from the studies by Chakravarty and Wolfe [5, 11].

Excess risk of NMSC among TNF-α antagonist users has biologic plausibility. TNF-α is a ubiquitous cytokine produced by many cells, including keratinocytes. When administered locally at high doses, TNF-α causes thrombosis and necrosis of blood vessels feeding tumour cells, and plays a role in CD8+ T-cell and NK-cell-mediated death of certain tumour cells [24–28]. Therefore, inhibiting this cytokine’s anti-tumour properties by using a TNF-α antagonist may lead to an increased risk of malignancy, including skin cancer.

We found a strong association between a prior history of malignancy, either haematological or solid, and subsequent risk of NMSC. This observation has been made by previous studies in populations of patients with non-Hodgkin’s lymphoma [29, 30], chronic lymphocytic leukaemia [31–33] and breast cancer [34, 35]. This association may be related to genetic factors, the pro-carcinogenic
effects of immunosuppressive therapies used to treat the primary cancer, or a combination of these. Other risk factors for NMSC that we identified, including older age, male gender, NSAID and glucocorticoid use, are supported by the results of prior studies (www.skincancer.org, www.SEER.cancer.gov, [12–15, 36]). In agreement with the findings of Wolfe and Michaud [11], our study showed that duration of TNF-α antagonist use was not a risk factor for the development of NMSC (OR 0.99 per duration interval, 95% CI 0.98, 0.99).

Our study has several strengths. The large size of the VA’s national databases allowed us to evaluate rare events in a large cohort of RA patients on DMARDS using stringent inclusion and exclusion criteria. Our study period of 10 years allowed us to examine outcomes that may have long latency periods such as skin cancer. As in previous studies [4–11], we adjusted for more common skin cancer risk factors such as age, gender and race (www.skincancer.org, www.SEER.cancer.gov, [12, 13]), although not for sun exposure [37]. However, we examined a more comprehensive list of other potential risk factors including a history of prior malignancy, glucocorticoid use and tobacco use, all of which have all been linked to NMSC [13–19, 38–40]. Due to the potential risk of malignancy with the TNF-α antagonists, many clinicians may avoid using these drugs in RA patients with a prior history of or new malignancy. To address this channelling bias, we used a time-varying propensity score, allowing for more comparable cohorts.

Our validation data are comparable with other studies looking at the accuracy of ICD-9 coding in administrative databases in terms of the range of κ values. In a study evaluating the accuracy of ICD-9 coding for various diagnoses, there was a 57% concordance between a validated diagnosis and ICD-9 code [41] similar to our study, which showed that 60% of ICD-9-CM for NMSC were correct. κ values vary greatly depending on the analysed diagnosis, but most show modest agreement. In another study evaluating the accuracy of ICD-9 diagnoses encompassing the Charlson comorbidity index, κ ranged from 0.34 to 0.87, mirroring the findings in our study [42].

Our study has limitations as well. Our patient population was mostly Caucasian and male, therefore, limiting the generalizability of our results. There is no generally accepted and validated, standardized tool to measure RA severity in administrative data, and RA severity may impact skin cancer risk. In order to adjust for RA severity, we included in our propensity score the number of orthopaedic procedures and number of IA glucocorticoid injections, two variables that have been shown to correlate with RA severity [43, 44]. We were unable to classify our population with NMSC into histological subtypes of basal and squamous cell carcinoma as these cancers are classified together under ICD-9 codes for NMSC terminology in the VA databases. Although our κ values for validation are comparable with other studies using administrative codes [41, 42], potential misclassification of NMSC may have affected our risk estimates.

Finally, it is possible that unmeasured confounders such as disease duration and dose of DMARDs such as MTX may have biased our results. We could not measure over-the-counter NSAID use, which may have underestimated our measured risk of NSAID use as a risk factor for NMSC. We did not adjust our analyses for sun exposure during childhood or adulthood or skin type. However, we expect that the distribution of these variables would not differ between populations receiving and not receiving TNF-α antagonists. Such unmeasured confounders are typical of the limitations associated with large administrative databases when used to attempt to answer these types of scientific questions. These limitations are, however, offset by the many strengths of such databases such as low cost, the immediate availability of data and power given the large size, to answer such questions. We acknowledge that we could not account for all possible variables, and caution that this is an observational study that draws no conclusions about cause and effect.

In conclusion, we have shown that TNF-α antagonist use may be associated with an increased risk of NMSC in patients with RA. This result should prompt rheumatologists to carefully and systematically screen all patients on TNF-α antagonists periodically for skin cancer and pre-cancerous lesions.

### Table 3 Individual TNF-α antagonists and risk of NMSC

<table>
<thead>
<tr>
<th>TNF-α antagonist</th>
<th>Total patients</th>
<th>Exposure (patient-years)</th>
<th>Number of NMSC</th>
<th>NMSC/patient-year</th>
<th>P-value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept</td>
<td>2781</td>
<td>6827</td>
<td>145</td>
<td>0.021</td>
<td>*</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1695</td>
<td>2583</td>
<td>92</td>
<td>0.036</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Infliximab</td>
<td>857</td>
<td>1674</td>
<td>47</td>
<td>0.028</td>
<td>0.260</td>
</tr>
</tbody>
</table>

*Reference category.

### Rheumatology key messages

- TNF-α antagonists may increase the risk of NMSC in patients with RA.
- Older males with RA and those with prior malignancies may be at higher risk.

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Supplementary data
Supplementary data are available at Rheumatology Online.

References


