**TITLE:** Melanoma risk in patients with rheumatoid arthritis treated with tumour necrosis factor alpha inhibitors: a systematic review and meta-analysis

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**Running Head:** Increased risk of melanoma in people with CLL

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**ABSTRACT**

Clinicians are concerned that treatment of rheumatoid arthritis (RA) with tumour necrosis factor alpha antagonists (TNFα biologics) may increase patients’ risk of melanoma compared with treatment with non-biologic disease-modifying antirheumatic drugs (nbDMARDS). We aimed to assess the melanoma risk in RA patients treated with TNFα biologics compared to RA patients treated with nbDMARDS. A secondary aim was to quantify the melanoma risk in RA patients treated with TNFα biologics compared with the general population. We conducted a systematicreview and meta-analysis searching Medline, Embase and the ISI Science Citation Index databases to January 2016. Cohort studies that permitted quantitative assessment of melanoma risk in RA patients treated with TNFα biologics compared with either RA patients treated with nbDMARDS or the general population or both were included. Data were pooled using a random effects model. From 812 articles, we identified six that met the inclusion criteria. Four studies reported on risk of melanoma in RA patients treated with TNFα biologics compared to those treated with nbDMARDS with a pooled effect estimate of 1.60 (95%CI 1.16-2.19). Five reported on risk of melanoma in RA patients treated with TNFα biologics compared with the general population, and the pooled effect estimate was 1.87 (95%CI 1.53-2.30). There was no significant heterogeneity in either analysis. This systematic review and meta-analysis does not allay clinician’s fears and, while awaiting further evidence from large collaborative studies, this patient population may benefit from regular skin checks and counselling to avoid excessive sun exposure.

 **Keywords:** TNFα, melanoma, meta-analysis, rheumatoid arthritis

**INTRODUCTION**

Clinicians are concerned that treatment of rheumatoid arthritis (RA) with tumour necrosis factor alpha antagonists (TNFα biologics) may increase patients’ risk of melanoma compared with treatment with non-biologic disease-modifying antirheumatic drugs (nbDMARDS) [[1](#_ENREF_1)]. Whilst most early studies evaluating risk of melanoma in people with RA irrespective of type of treatment did not show an increased risk compared to the background population risk [[2](#_ENREF_2)], treatment regimens have evolved in recent decades, and studies conducted more recently have reported higher risk of melanoma in RA patients than in the general population [[3](#_ENREF_3), [4](#_ENREF_4)]. TNFα biologics were first introduced in 1998 [[5](#_ENREF_5)] and registries have been established to examine biologic use and cancer risk [[6](#_ENREF_6)] due to increased malignancy concerns.

RA patients treated with TNFα biologic therapy experience profound immunomodulation [[7](#_ENREF_7)] and thus may be at increased risk of melanoma, an immunogenic cancer, similar to solid organ transplant recipients or those with human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS) [[8](#_ENREF_8), [9](#_ENREF_9)] with compromised immunity. A meta-analysis conducted in 2011, pooling the results of only two available studies, reported a combined estimate of the risk of melanoma in RA patients treated with TNFα biologics vs. biologics-naive patients of 1.79 (95% CI 0.92, 2.67) [[6](#_ENREF_6)]. A meta-analysis of melanoma risk in nbDMARD-treated RA patients compared with the general population reported a pooled Standardised Incidence Ratio (SIR) of 0.95 (95% CI 0.86, 1.04) (n=11 studies) [[10](#_ENREF_10)]. That meta-analysis specifically excluded patient populations known to be exposed to TNFα biologics [[11](#_ENREF_11), [12](#_ENREF_12)] and thus showed that RA patients treated with nbDMARDS are not at increased risk of melanoma compared with the general population. To date there has been no combined analysis of estimates of the risk of melanoma in RA patients treated with TNFα biologics compared with the general population, yet this is needed so that comparisons with other patient populations treated with TNFα biologics, such as inflammatory bowel disease patients [[13](#_ENREF_13)] can be made. This systematic review and meta-analysis therefore aimed to synthesize the available evidence on the melanoma risk in RA patients treated with TNFα biologics compared with those treated with nbDMARDS. A secondary aim was to quantify the melanoma risk in TNFα biologics-treated RA patients compared with the general population.

**Methods**

The systematic review and meta-analysis was conducted in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines for reviews of observational

Studies (MOOSE) [[14](#_ENREF_14)] (see checklist in Online Resource 1).

***Data Sources and Searches***

Eligible studies published between 1st January 1998 and January 2016 were identified by searching the Medline 1950 (U.S. National Library of Medicine, Bethesda, MD) database using PubMed software as the search interface; Embase 1966 database (Elsevier Science, Amsterdam, Holland) using the Embase search interface; and the ISI Science Citation Index using the ISI Web of Science search interface. We used the following medical subject headings terms or text words (both the United States and United Kingdom spellings): melanoma, cancer, neoplasms, rheumatoid arthritis, RA, rheumatic diseases, aetiology, cohort (Appendix 1 – search terms). Studies that had been commonly cited in the literature and review articles were also included as citation search terms in the ISI Science Citation Index (1990 to present) to identify subsequent studies that had referenced them. We did not search for abstracts, unpublished studies or other such literature since the data reported is often preliminary and may not be representative of the final study result [[15](#_ENREF_15)]. The search was not limited to studies published in English. We read the abstracts of all identified studies to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine if they met study inclusion criteria. Eligible studies were also identified by hand-searching the reference lists of retrieved articles, including reviews.

***Study Selection***

We included all studies that were based on cohorts of patients diagnosed with RA that permitted quantitative assessment of the risk of melanoma in RA patients treated with TNFα biologics compared with those treated with nbDMARDS or the general population. Studies that reported different measures of relative risk (RR), namely Hazard Ratio (HR), Odds Ratio (OR), and Standardised Incidence Ratio (SIR) were included. We excluded randomized controlled trials (RCTs) because they are typically conducted using small numbers of participants over a short duration and for rare outcomes like melanoma larger sample sizes and longer-term follow-up is required. RCTs also have strict inclusion criteria, making it difficult to generalise the trial findings to other more heterogeneous patient populations. Finally, screening of potential subjects before (and surveillance during) clinical trials may eliminate patients at highest risk of developing melanoma in the short-term or alternatively could result in surveillance bias.

 Any discrepancies between investigators on inclusion of a study were resolved by joint evaluation of the manuscript. When multiple reports were published on the same population or subpopulation, we included in the meta-analysis the report with the longest follow-up duration or the most comprehensive data.

***Data Extraction and Quality Assessment***

Two investigators (CO, LK) independently abstracted data from identified studies using a standardised data abstraction form, with inconsistencies resolved by consensus. The following information was recorded for each study: study design, location, years of data collection, source and definition of cohort, number of cases, person-year duration of follow-up, age of study population, variables used for statistical adjustment, point estimates (odds ratio (OR), hazard ratio (HR), or standardized incidence ratio (SIR)), and 95% confidence intervals (95% CI). We evaluated the quality of primary studies using the Newcastle–Ottawa Scale [[16](#_ENREF_16)], a validated technique for assessing the quality of observational studies.

***Data synthesis and analysis***

To pool individual study estimates for the risk of melanoma in RA patients, we used the method of DerSimonian and Laird [[17](#_ENREF_17)], using a random effects model. Statistical heterogeneity among studies was assessed using the Q statistic [[18](#_ENREF_18)] (significance level at P<0.10), and inconsistencies were quantified using the I2 statistic [[19](#_ENREF_19)]. We performed a sensitivity analysis by omitting one study at a time, and calculated the pooled RR for the remaining studies to evaluate whether the results could have been affected markedly by a single study. Finally, publication bias was evaluated through visual inspection of a funnel plot and with Begg’s and Egger’s tests [[20](#_ENREF_20), [21](#_ENREF_21)]. We calculated the absolute risk of melanoma in RA patient treated with TNFα biologics in several populations (USA, UK, Denmark, Sweden, Australia) using age-standardized incidence rates sourced from Globocan 2012 [[22](#_ENREF_22)]. All statistical analyses were performed using Stata Version 10 (Stata Corporation, College Station, TX).

**RESULTS**

***Search***

Details of the selection process for the eligible studies are shown in Fig. 1. Of 812 titles identified, a total of six studies eligible to be included in our systematic review were identified [[3](#_ENREF_3), [4](#_ENREF_4), [11](#_ENREF_11), [12](#_ENREF_12), [23](#_ENREF_23)]; four studies reported an estimate for risk of melanoma in RA patients treated with TNFα biologics compared to those treated with nbDMARDS [[3](#_ENREF_3), [4](#_ENREF_4), [23](#_ENREF_23)], and five reported an SIR for risk of melanoma in RA patients treated with TNFα biologics compared with the general population [[3](#_ENREF_3), [11](#_ENREF_11), [12](#_ENREF_12), [23](#_ENREF_23)]. A summary of studies excluded after detailed review is provided in Supplementary Table 1. Two studies included patients treated with Anakinra (an interleukin-1 (IL-1) receptor antagonist) in their bDMARD cohorts, however this constituted only 2% [[11](#_ENREF_11)] and 2.5% [[3](#_ENREF_3)] of included patients, and the latter study reported results for individual drugs in their comparison with the nbDMARD treatment group (not however in their comparison with the general population). One study presented estimates for different types of TNFα biologics (etanercept, infliximab, adalimumab) [[3](#_ENREF_3)].

***Characteristics of the included studies***

The main characteristics of the included studies are listed in Table 1. Studies were published between 2005 and 2015. Three studies were conducted in Northern Europe [[4](#_ENREF_4), [12](#_ENREF_12), [23](#_ENREF_23)], two in North America [[3](#_ENREF_3), [11](#_ENREF_11)] and one in Australia [[24](#_ENREF_24)]. Mean or median follow-up time for the cohorts ranged from 2.1 to 4.8 years. Two studies reported on overlapping cohorts [[4](#_ENREF_4), [12](#_ENREF_12)], however each reported a different comparison (i.e. in the study reported by Askling et al. [[12](#_ENREF_12)] the comparison group was the general population whilst for Raaschou et al. [[4](#_ENREF_4)] the comparison group was RA patients treated with nbDMARDS), and thus both were included in the review. With the exception of one study which relied on administrative claims data [[11](#_ENREF_11)], all melanomas diagnoses were established through linkage with cancer registries. Only one [[3](#_ENREF_3)] of the four studies [[3](#_ENREF_3), [4](#_ENREF_4), [23](#_ENREF_23), [24](#_ENREF_24)] that reported on risk of melanoma in RA patients treated with TNFα biologics compared with patients treated with nbDMARDS had adjusted for a measure of disease severity at baseline.

***Quality Assessment***

Five [[3](#_ENREF_3), [4](#_ENREF_4), [12](#_ENREF_12), [23](#_ENREF_23), [24](#_ENREF_24)] of the six studies scored 8 out of a possible score of 9 using the Newcastle-Ottawa quality assessment scale for cohort studies [[16](#_ENREF_16)]; the remaining study scored 7 points [[11](#_ENREF_11)].

***Outcome***

The pooled effect estimate for studies reporting on melanoma risk in RA patients treated with TNFα biologics compared with RA patients treated with nbDMARDS was 1.60 (95% CI 1.16-2.16) (Fig. 2). Omitting one study at the time resulted in summary estimates ranging from 1.50 (95% CI 1.07–2.11) with the omission of Wolfe et al. [[3](#_ENREF_3)] to 1.78 (95% CI, 1.04–3.05) with the omission of Raaschou et al. [[4](#_ENREF_4)]. There was no evidence of publication bias (Begg P=0.45; Egger P=0.72).

The pooled SIR (pSIR) for studies reporting on risk of melanoma in RA patients treated with TNFα biologics compared with the general population was 1.87 (95% CI 1.53-2.30) (Fig. 3). The summary estimate was not materially influenced by excluding one study at a time, with the pSIR ranging from 1.71 (95% CI 1.34–2.18) with the omission of Setoguchi et al. [[11](#_ENREF_11)] to 2.07 (95% CI, 1.55–2.77) with the omission of Wolfe et al. [[3](#_ENREF_3)]. Again there was no evidence of publication bias (Begg P=0.46; Egger P=0.38). There was no significant heterogeneity for either analysis (Figs. 2 and 3).

In absolute terms, the raised risk would equate to an estimated additional 12 cases per 100,000 RA patients treated with TNFα biologics per year in the USA, 16 in Denmark or Sweden and 30 in Australia above what would be observed in the general population.

**DISCUSSION**

We have examined the available evidence from observational studies reporting on the risk of melanoma in RA patients treated with TNFα biologics and report a 60% increased risk compared with patients treated with nbDMARDS and a 90% increased risk compared with the general population.

A previous meta-analysis for the comparison with patients treated with nbDMARDS [[6](#_ENREF_6)] had pooled the results of two studies, an interim report from the Swedish biologics register (Anti-Rheumatic Therapy in Sweden, ARTIS) [[25](#_ENREF_25)] and a report by Wolfe and colleagues [[3](#_ENREF_3)] using data from the US National Data Bank for Rheumatic Diseases (NDB). The combined estimate of those two studies was 1.79 (95% CI 0.92, 2.67) [[6](#_ENREF_6)]. Our meta-analysis extends that analysis by including a more recent report from the ARTIS study [[4](#_ENREF_4)] (including an additional 31,530 person-years after TNFα biologics treatment) as well as a report from the national Danish DANBIO database [[26](#_ENREF_26)] (15,592 person-years after TNFα biologics treatment) and the Australian Rheumatology Association Database (ARAD) [[24](#_ENREF_24)] (5,752 person-years after TNFα biologics treatment), resulting in a more precise risk estimate. A combined estimate from observational studies of the risk of melanoma in RA patients treated with TNFα biologics compared with the general population has not previously been reported. Notably our findings are not discordant with a pooled analysis of 36 RCTs examining the risk of melanoma in RA patients treated with Adalimumab compared with the general public, which reported a pooled SIR of 1.5 (95% CI 0.84-2.47) [[27](#_ENREF_27)].

Meta-analyses of short-term clinical trials [[28](#_ENREF_28)] and long-term observational studies [[6](#_ENREF_6)] in patients with rheumatoid arthritis have not demonstrated a marked increase in the risk of all-site cancer associated with use of TNFα biologics compared with nbDMARDS, but the observational data, in aggregate, suggest an increased risk of keratinocyte skin cancers [[29](#_ENREF_29)] as well as melanoma [[6](#_ENREF_6)]. The role of TNFα antagonist treatment in cancer development is complex since it exerts both pro- and anti-carcinogenic effects [[7](#_ENREF_7)]. TNF may promote tumour development and progression through inflammatory pathways [[30](#_ENREF_30)], but it is also involved in the immunosurveillance of cancer cells [[31](#_ENREF_31)].

All studies included in our meta-analysis received a high quality score using the Newcastle-Ottawa quality assessment scale for cohort studies [[16](#_ENREF_16)]. A limitation of our analyses was the potential for publication bias. Our analyses may have been subject to publication bias because we did not search for unpublished studies, abstracts or other such literature, but on the other hand, inclusion of only results from peer-reviewed studies gave greater assurance of the quality of those data we did include. Several studies that examined cancer outcomes in a cohort of RA patients treated with TNFα biologics were not eligible to be included in our review because they did not provide an estimate of the association for melanoma. Two of these reports [[32](#_ENREF_32), [33](#_ENREF_33)] that examined risk in a TNFα biologics-treated group compared to a nbDMARD treated group reported a melanoma case in the treatment group but not in the comparison group. A third report that compared incidence rates in a TNFα biologics group (n=1114) compared with the general population did not report any melanoma cases in the treatment group [[34](#_ENREF_34)] after an average follow-up time of 23 months. Two other excluded studies [[35](#_ENREF_35), [36](#_ENREF_36)] reported on solid cancers overall but it was not clear from these reports if melanomas cases were specifically assessed; this may have led to outcome reporting bias [[37](#_ENREF_37)] if melanoma cases were observed but not analysed or reported because of non-significant or null results, resulting in an overestimate of a more modest true association. Conversely, the studies that were included in our review may not have sufficiently covered the latent period for melanoma development, with a maximum median follow-up period of 4.8 years, and this may had led to an underestimation of the association.

A further limitation of registry-based reporting is the challenge of full case ascertainment as well as case verification. Two of the included studies [[3](#_ENREF_3), [11](#_ENREF_11)] ascertained melanoma diagnosis using different methods for the RA cohort and the comparison population (i.e. internal ascertainment for the RA cohort and Registry ascertainment for the general population comparison), which may have led to more complete case ascertainment in the RA population. The remaining studies used linkage to national cancer registries for both the RA cohort and the comparison population. Our findings may not be generalizable to all populations since the combined estimates were heavily weighted by the results of studies conducted in the US and Sweden, and furthermore, underregistation of melanoma is a limitation of US National Cancer Institute SEER (Surveillance, Epidemiology, and End-Results) data (estimates range from 30-40%) [[38](#_ENREF_38)]. Finally, limited control of confounding may have influenced the results since all but one of the included studies [[4](#_ENREF_4)] did not have information on key melanoma risk factors such as skin type, ethnicity, prevalence of melanocytic nevi, or family history. These factors, however, are not associated with RA and are thus unlikely to have influenced the observed associations.

Only one [[3](#_ENREF_3)] of the three studies [[3](#_ENREF_3), [4](#_ENREF_4), [26](#_ENREF_26)] that reported on risk of melanoma in RA patients treated with TNFα biologics compared with patients treated with nbDMARDS had adjusted for a measure of disease severity at baseline, and only two studies [[24](#_ENREF_24), [26](#_ENREF_26)] reported sufficient data to determine baseline differences in disease severity between the comparison groups. Whilst a positive association has been reported for RA disease severity and risk of lymphoma [[39](#_ENREF_39)], however, it has not been reported for melanoma and thus is unlikely to have influenced the observed associations.

In conclusion, analogous to other immunosuppressed patient groups, RA patients treated with TNFα biologics appear to be at increased risk of melanoma and therefore may benefit from regular screening of the skin for suspicious pigmented lesions. As yet unknown is whether treatment with TNFα biologics increases the recurrence rate of melanoma or the risk of second primary in those with a previous melanoma; to date there is only anecdotal information from case series [[40](#_ENREF_40)]. Further large-scale cohort studies with patient-level clinical data have the potential to better inform the management of melanoma risk in RA patients treated with immunosuppressive therapies by better understanding the impact of immunosuppression, as well as how known risk factors operate differently in these populations versus the general population.

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**Table 1**. Characteristics of the six studies included in the meta-analysis of risk of melanoma in patients treated with TNF alpha antagonists.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Location (study period)** | **Cohort description** | **Cases/****Cohort (N)** | **Mean or median diagnosis age (years)** | **Mean or median follow-up (years)** | **Comparison population (measure of effect)** | **Exposure definition** | **Effect Estimate** | **Adjustment for confounding factors** |
|  |  |  |  |  |  |  |  |  |  |
| Askling et al., 2005 | Sweden(1990-2003) | Population based cohort RA patients treated with TNFα antagonists | 1/4160 | NR | Mean 2.3 | General population (SIR) | TNFα antagonist treated, EaIbAc | 0.3 (0.0-1.8) | Age, sex, calendar period |
|  |  |  |  |  |  |  |  |  |  |
| Setoguchi et al., 2006 | United States and Canada(1994-2004) | RA patients ≥=65 years with at least 1 prescription of any DMARD or MTX after diagnosis of RA | 29/7830(1/1152 biologic treated) | Mean: 71.4 | NR | General population (SIR) | biologic treated, Ea Ib Ac Ad and/or MTX | 2.3 (1.55-3.22) | Age and sex |
|  |  |  |  |  |  |  |  |  |  |
| Wolfe et al., 2007 | United States(1998-2005) | US National Data Bank for Rheumatic Diseases longitudinal study | 32/13869 | Mean 58.5 | Mean 3.0 | RA patients not treated with TNFα antagonists (OR)General population (SIR) | TNFα antagonist treated, Ea TNFα antagonist treated, IbTNFα antagonist treated, AcAny TNFα antagonist TNFα antagonist treated,Ea Ib Ac Ad | 2.40 (1.00-5.80)2.60 (1.00-6.70)0.80 (0.10-6.60)2.30 (0.90-5.40)1.70 (1.30-2.30) | Adjusted for age, sex, education, smoking history, baseline Patient Activity Scale score, and baselineprednisone useAge and sex |
|  |  |  |  |  |  |  |  |  |  |
| Dreyer et al., 2012  | Denmark(2000-2008) | DANBIO database (5345 TNFα antagonist treated, 4351 never treated with TNFα antagonists) | 6/5345biologic treated3/4351 nobiologics | Mean 54.3Mean: 61.2 | Mean 2.1Mean 2.9 | RA patients not treated with TNFα antagonists (HR)General population (SIR) | Ever TNFα antagonist treated | 1.54 (0.37-6.34)1.57 (0.70-3.49) | Age, sex, calendar timeAge, sex, calendar time |
|  |  |  |  |  |  |  |  |  |  |
| Raaschou et al., 2013 | Sweden (2001-2010) | Population based cohort Swedish Outpatient Register, ARTIS | 38/10878biologic treated113/42198 no biologics | Median: 52Median: 62 | Median 4.8Median 4.6 | RA patients not treated with biologics (HR) | Ever TNFα antagonist treated | 1.50 (1.00-2.20) | Stratified for year of inclusion and adjusted for sex, age, country of birth, personal history of non-melanoma skin cancer in situ, family history of melanoma, educational level, and comorbidities during follow-up  |
|  |  |  |  |  |  |  |  |  |  |
| Buchbinder et al., 2015 | Australia(2008-2010) | Australian Rheumatology Association Database | 15/2237(10/2145 biologic treated) | Mean: 73.4 | Mean 2.5 | RA patients not treated with biologics (RR)General population (SIR) | Ever TNFα antagonist treated, Ea Ib Ac | 0.54 (0.12-2.40)2.03 (1.09-3.78) | Age, sex, calendar year, smoking status, methotrexate use and prior malignancy |
|  |  |  |  |  |  |  |  |  |  |

aEtanercept b Infliximab cAdalimumab dAnakinra (IL-1R antagonist); only 2.5% of biologics in Wolfe et al. and 2% in Setoguchi et al. were Anakinra

**Fig. 1** Flow chart of literature search for studies on the association between TNFα biologics treatment in rheumatoid arthritis and melanoma

**Fig. 2** Forest plot of the association between TNFα biologics treatment in rheumatoid arthritis and melanoma compared with patients treated with nbDMARDS. Each line represents an individual study result with the width of the horizontal line indicating 95% CI, the position of the box representing the point estimate, and the size of the box being proportional to the weight of the study (I=infliximab; E=etanercept; A= adalimumab)

**Fig. 3** Forest plot of the association between TNFα biologics treatment in rheumatoid arthritis and melanoma compared with the general population. Each line represents an individual study result with the width of the horizontal line indicating 95% CI, the position of the box representing the point estimate, and the size of the box being proportional to the weight of the study