Rheumatoid arthritis, anti-tumour necrosis factor treatment, and risk of squamous cell and basal cell skin cancer: cohort study based on nationwide prospectively recorded data from Sweden

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ABSTRACT

OBJECTIVE

To investigate the risk of squamous cell and basal cell skin cancer in patients with rheumatoid arthritis naive to biologic drugs, in patients starting tumour necrosis factor (TNF) inhibitor treatment, and in the general population.

DESIGN

Population based cohort study.

SETTING

Nationwide data from Sweden.

PARTICIPANTS

Cohort of patients with rheumatoid arthritis naive to biologics (n=46 409), cohort of patients with rheumatoid arthritis starting TNF inhibitor treatment as first biologic in 1998-2012 (n=12 558), and matched general population comparator cohort, identified through national quality of care and health registers.

MAIN OUTCOME MEASURE

Hazard ratio of first in situ or invasive squamous cell skin cancer (1998-2012) and first basal cell cancer (2004-12).

RESULTS

For basal cell cancer, the hazard ratio was 1.22 (95% confidence interval 1.07 to 1.41) comparing biologics-naive rheumatoid arthritis patients with the general population and 1.14 (0.98 to 1.33; 236 *v* 1587 events) comparing TNF inhibitor treated patients with biologics-naive patients. For squamous cell cancer, the hazard ratio was 1.88 (1.74 to 2.03) comparing biologics-naive rheumatoid arthritis patients with the general population and 1.30 (1.10 to 1.55; 191 *v* 847 events) comparing TNF inhibitors with biologics-naive patients; the latter translated to an annual number needed to harm in the order of 1600. Among people with a history of squamous cell or basal cell cancer, TNF inhibitors did not further increase risks.

CONCLUSION

A small to moderately increased risk of basal cell cancer was seen in biologics-naive rheumatoid arthritis patients, with no further effect of TNF inhibitors. For squamous cell cancer, the risk was nearly doubled in biologics-naive patients, with a further 30% increase in risk among patients treated with TNF inhibitors; this translates to one additional case for every 1600 years of treatment experience, assuming that this association reflected causality. Vigilance regarding skin malignancies may be advisable in rheumatoid arthritis, irrespective of TNF inhibitor treatment. Most of the increase in risk for non-melanoma skin cancer in patients with rheumatoid arthritis treated with TNF inhibitors originates from factors other than that treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

In addition to its role in inflammation, tumour necrosis factor (TNF) plays a role in tumour biology

Concerns exist that TNF inhibitors may increase the risk of cancer, particularly non-melanoma skin cancer (NMSC)

Studies to date show conflicting results and are often hampered by low numbers of NMSC and lack of data on histopathology

WHAT THIS STUDY ADDS

Patients with rheumatoid arthritis are at a 20% increased risk of basal cell cancer (BCC) and a near doubled risk of squamous cell cancer (SCC) compared with the general population

Patients treated with TNF inhibitors have a moderately increased risk of BCC that is not statistically significant after adjustments for demographics and comorbidities and a 30% increased risk of SCC compared with patients never treated with biologics

Vigilance for skin lesions is advisable in patients with rheumatoid arthritis, although most NMSCs occur for other reasons than the TNF inhibitor treatment

If the observed association with TNF inhibitors were to reflect causality in its entirety, there would be one extra annual case of SCC for every 1600 patients treated

Introduction

Tumour necrosis factor (TNF) inhibitors have become standard of care in the treatment of rheumatoid arthritis and other chronic inflammatory diseases. In addition to its role in inflammation, TNF plays a role in tumour biology.[1] Concerns have been expressed that TNF inhibitors may increase the risk of cancer, particular non-melanoma skin cancers (NMSC), which are known to be associated with states of immune perturbation.[2 3] Organ transplantation has been associated with a 10-fold risk of basal cell cancer and a 50-200-fold increased risk of squamous cell cancer.[4-7] Studies in patients with rheumatoid arthritis naive to biologic drugs (listed in supplementary table A) have indicated a 20-80% increased risk of NMSC compared with the general population.[8-12]

TNF inhibitor treatment may influence the risk of NMSC in rheumatoid arthritis. Such associations have been described in case reports of rapidly evolving squamous cell cancer after TNF inhibitor treatment is started,[13 14] and a large meta-analysis of clinical trial data indicated a doubled risk of NMSC during the typically short timeframes of clinical trials.[15] Observational studies of rheumatoid arthritis patients treated with TNF inhibitors have reported mixed results, with some suggesting an increased risk of NMSC[10 16-18] and others not.[12 19] In most of these studies, NMSC has been studied without differentiating in situ from invasive

lesions or squamous cell from basal cell cancer. Whereas most studies have reported on overall risks, stratification by follow-up time is important as it might reconcile some of the discrepancies in the studies published to date.

Our aim was to investigate the relative risk of NMSC (first squamous cell cancer and first basal cell cancer, separately) with rheumatoid arthritis and TNF inhibitor treatment. We therefore compared biologic-naive patients with rheumatoid arthritis with people from the general population as well as patients treated with TNF inhibitors.

Methods

Study design and setting

Provision of healthcare in Sweden is funded by taxation. Patients with rheumatoid arthritis are typically treated by rheumatologists. During the study period, an estimated 25% of all patients with rheumatoid arthritis in Sweden were being or had been treated with TNF inhibitors.[20] Through linkages enabled by personal identification numbers, we gathered information about treatment, outcomes, and covariates from national administrative and clinical registers on demographics, morbidity, and mortality between 1 January 1998 and 31 December 2012.

Data sources

The registers used in this study are described in supplementary table B and have been described in detail elsewhere.[21] In brief, the Swedish Biologics Register (ARTIS) is a subset of the Swedish Rheumatology Quality Register, enriched with data from other national registers. It includes adult patients starting any anti-rheumatic biological treatment. The coverage of the Swedish Biologics Register ARTIS/SRQ is approximately 90%.[22] At start of treatment and at follow-up visits, the rheumatologist enters details of the disease activity and anti-rheumatic treatment. The Swedish National Cancer Register was established in 1958. Reporting of incident cancers is mandatory, resulting in an estimated coverage of greater than 95%.[23] The register contains data on date of cancer and on morphology and type of cancer according to the international classification of diseases (supplementary table C). All consecutive skin tumours are reported, both invasive and in situ. Basal cell cancers have been reported to the register nationwide since 2004.

Study population

Squamous cell cancer

We identified all people with a minimum of two visits with rheumatoid arthritis as main or contributory diagnosis in non-primary outpatient care between 1 January 2001 and 31 December 2012 (n=65 113; see supplementary figure A). We required at least one of these visits to be at a department of rheumatology or internal medicine, and the second visit served as the inclusion date. We excluded people who, before the start of follow-up, had ever been diagnosed as having juvenile arthritis, ankylosing spondylitis, psoriatic arthritis, or systemic lupus erythematosus. We also excluded people with a history of organ transplantation or invasive malignancy other than NMSC before the start of follow-up. For the primary outcome, we excluded people with a history of the outcome before the start of follow-up.

By linkage to the Swedish Biologics Register ARTIS/SRQ, we excluded people with any biologic treatment before the inclusion date, leaving 46 409 biologics-naive patients in the squamous cell cancer study population. Through the register, we identified all patients who started TNF inhibitor treatment as first ever biologic therapy between 1 January 1998 and 31 December 2012 (n=14 072), leaving 12 558 TNF inhibitor treated patients in the squamous cell cancer study population after exclusion of those with organ transplantation or malignancy. No patient was included on the basis on ongoing treatment. TNF inhibitor treatment encompassed treatment with any of the five TNF inhibitors registered in Sweden during the study period: adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab.

Basal cell cancer

Basal cell cancers were not reported in the Cancer Register until 1 January 2004 at the earliest. Using similar linkage and exclusions to above, we identified 43 675 biologics-naive patients and 8827 TNF inhibitor treated patients.

General population comparator cohorts

We matched general population comparators (10:1) on sex, year of birth, and county of residence to the biologics-naive subsets of the squamous cell and basal cell cancer study populations. Comparators were assigned the same date of inclusion as their matched rheumatoid arthritis patient. Following similar exclusions to above, we had 379 666 comparators for the squamous cell cancer study population and 364 584 for the basal cell cancer study populations.

Exposure

We used two exposure contrasts: biologics-naive patients with rheumatoid arthritis compared with the general population, and TNF inhibitor treated compared with biologics-naive rheumatoid arthritis patients.

Outcomes

We defined the primary outcome as a first in situ or invasive squamous cell cancer or a first basal cell cancer among people with no history of the outcome before the start of follow-up. We also evaluated in situ and invasive squamous cell cancers separately. Secondary outcomes included first in situ or invasive squamous cell cancer or first basal cell cancer among people with a history of the outcome before the start of follow-up.

Follow-up

Follow-up among the TNF inhibitor treated patients began at the start of the first TNF inhibitor. We considered patients to be at risk even if TNF inhibitor treatment

was terminated ("ever exposed"). Follow-up among the biologics-naive patients began at the first date of inclusion in the cohort—earliest 1 January 2001 in the analyses of squamous cell cancer and earliest 1 January 2004 in the analyses of basal cell cancer. Follow-up ended at the occurrence of the outcome, malignancy other than the outcome, organ transplantation, start of any biologic treatment (biologics-naive cohort), emigration, death, or end of study period (31 December 2012).

Potential confounders

We identified the following potential confounders through register linkages as described in supplementary table B and elsewhere[21]: age, sex, birth year, country of birth, county of residency, educational level, and comorbidities up until the start of follow-up (hospital admissions/outpatient visits for chronic obstructive pulmonary disease, ischaemic heart disease, diabetes mellitus, knee/hip joint replacement surgery, psoriatic disease, and any other diagnosis of benign skin disease except actinic keratosis).

Statistical methods

We used Cox regression to estimate hazard ratios and their corresponding 95% confidence intervals, using follow-up time as the timescale. Effectively, our design assessed TNF inhibitor treatment as a time dependent covariate, as more than 99% of the TNF inhibitor treated patients alive after 1 January 2001 were also (and first) captured in the rheumatoid arthritis cohort of 65 113 people from which the biologics-naive study populations were identified.

In the analyses of TNF inhibitor treated versus biologics-naive rheumatoid arthritis, the final model was adjusted for age, sex, birth year, country of birth, county of residency, educational level, and comorbidities up until the start of follow-up. The analyses of biologics-naive rheumatoid arthritis versus the general population were adjusted for age, sex, birth year, country of birth, county of residency, and educational level but not for comorbidities, as these mostly pertained to time points after the onset of rheumatoid arthritis.

We did several sensitivity analyses. Firstly, by altering the definition of the outcomes, we assessed the primary outcomes by site of the malignant lesion (first lesion on head versus first lesion on body). Secondly, by altering the definition of biologics-naive comparator, we assessed the robustness of the hazard ratio for first in situ or invasive squamous cell cancer by using three subcohorts nested within the original biologics-naive rheumatoid arthritis cohort. Thirdly, we assessed the primary outcomes by using two alternative definitions of exposure: restricting the TNF inhibitor cohort to patients with ongoing treatment for at least 180 days after starting treatment (that is, without a registered stop date in the Swedish Biologics Register ARTIS/SRQ within that period) and using an "as treated" definition of exposure whereby only follow-up time within the registered treatment periods and outcomes during those periods (+90 days) was included. Fourthly, we analysed use of oral corticosteroids, ciclosporin, cyclophosphamide, and/or azathioprine during follow-up as a potential confounder among TNF inhibitor treated and biologics-naive patients who were incident rheumatoid arthritis cases and those starting TNF inhibitors in 2005 or later.

The number needed to harm (NNH) can be defined as the number of people who need to be exposed to a risk factor during a certain time period to cause one excess event as the result of exposure.[24] We calculated it as NNH=1/(crude incidence among unexposed×(relative risk−1)).

We tested the proportional hazards assumption (and found it not to be violated) by introducing an interaction term of exposure and log of follow-up time in the models. We used the SAS software package, version 9.2.

Patient involvement

Although patient involvement in the clinical register is established, patients were not explicitly involved in the research question, the outcome measures, or the design or implementation of the study. Patient involvement will be important for the dissemination of the results.

Results

Mean follow-up for squamous cell cancer was 5.9 years for patients starting TNF inhibitors and 5.1 years for biologics-naive rheumatoid arthritis patients. We censored 9814 (21%) of the biologics-naive patients owing to start of TNF inhibitors during follow-up, 6179 (13%) died, and 3103 (7%) were censored owing to solid malignancy other than the outcome. Eight hundred and nineteen (7%) of the TNF inhibitor treated patients died, and 706 (6%) were censored owing to solid malignancy other than the outcome. As expected, follow-up was slightly shorter in the basal cell cancer study population (table 1).

Squamous cell cancer

Biologics-naive rheumatoid arthritis versus the general population

We detected 847 first invasive or in situ squamous cell cancers in the biologics-naive cohort, compared with 4168 occurring in the general population comparator. The hazard ratio for squamous cell cancer was 1.88 (95% confidence interval 1.74 to 2.03) (table 2 and fig 1).

TNF inhibitor treated versus biologics-naive rheumatoid arthritis

We detected 191 first invasive or in situ squamous cell cancers in the TNF inhibitor treated cohort. Compared with the biologics-naive cohort, the age and sex adjusted hazard ratio was 1.43 (1.22 to 1.69). Further adjustment for demographics and comorbidities resulted in a hazard ratio of 1.30 (1.10 to 1.55) (table 3). This remained consistent across strata defined by sex, age at start of TNF inhibitor treatment, time since start of TNF inhibitor treatment, and year of TNF inhibitor treatment start (table 4).

Based on the crude incidence of the biologics-naive cohort standardised to the age distribution of the TNF

Table 1 | Baseline characteristics of population based Swedish cohorts used to study squamous cell cancer* and matched general population comparators, and basal cell cancer† and matched general population comparators. Values are numbers (percentages) unless stated otherwise

	Squamous cell cancer			Basal cell cancer		
Characteristics	TNF inhibitor treated (n=12 558)	Biologics-naive RA (n=46 409)	General population (n=379 666)	TNF inhibitor treated (n=8827)	Biologics-naive RA (n=43 675)	General population (n=364 584)
Female sex	9473 (75.4)	33 202 (71.5)	270 623 (71.3)	6601 (74.8)	31 216 (71.5)	259 816 (71.3)
Mean (SD) age at entry, years	55.2 (13.3)	60.9 (14.7)	59.4 (14.7)	55.3 (13.6)	61.6 (14.7)	60.8 (14.5)
Entry year, median	2006	2004	2004	2008	2005	2005
Mean (SD) follow-up, years	5.9 (3.8)	5.1 (3.6)	6.5 (3.7)	4.2 (2.7)	4.7 (3.1)	5.8 (3.0)
Country of birth:						
Nordic	11 774 (93.8)	43 603 (94.0)	348 551 (91.8)	8232 (93.3)	41 013 (93.9)	333 155 (91.4)
Other (including missing)	784 (6.2)	2806 (6.0)	31 115 (8.2)	595 (6.7)	2662 (6.1)	31 429 (8.6)
≤9 years' education	3824 (30.5)	20 009 (43.1)	140 142 (36.9)	2456 (27.8)	18 456 (42.3)	126 021 (34.6)
Comorbidities before start of follow-up:						
Chronic obstructive pulmonary disease	302 (2.4)	1581 (3.4)	6627 (1.8)	233 (2.6)	1687 (3.9)	6650 (1.8)
Diabetes mellitus	679 (5.4)	2857 (6.2)	16 239 (4.3)	507 (5.7)	2934 (6.7)	16 329 (4.5)
Ischaemic heart disease	705 (5.6)	4493 (9.7)	26 832 (7.1)	495 (5.6)	4571 (10.5)	25 892 (7.1)
Joint surgery	3267 (26.0)	8277 (17.8)	17 588 (4.6)	1964 (22.2)	8292 (19.0)	17 442 (4.8)
Dysplastic naevi	115 (0.9)	276 (0.6)	2007 (0.5)	93 (1.1)	333 (0.8)	1913 (0.5)
Any benign skin disease‡	660 (5.3)	1748 (3.8)	11 247 (3.0)	606 (6.9)	2084 (4.8)	12 248 (3.4)
Squamous cell cancer	0 (0)	0 (0)	0 (0)	49 (0.6)	494 (1.1)	726 (0.2)

RA=rheumatoid arthritis; TNF=tumour necrosis factor.
*RA patients starting TNF inhibitor as first ever biologic drug 1998-2012; RA patients identified 2001-12 (censored at start of first biologic drug).
†RA patients starting TNF inhibitor as first ever biologic drug 2004-12; RA patients identified 2001-12 (start of follow-up earliest 1 January 2004, censored at start of first biologic drug).
‡Excluding actinic keratosis.

Table 2 | Occurrence and hazard ratios of invasive or in situ squamous cell cancer in 46 409 biologics-naive Swedish rheumatoid arthritis (RA) patients compared with 379 666 general population comparators, and of basal cell cancer in 43 675 biologics-naive Swedish RA patients compared with 364 584 general population comparators

	No of events (person years of follow-up; No of events/100 000 person years)		
Cancer type	Biologics-naive RA	General population	Hazard ratio* (95% CI)
Squamous cell cancer	847 (238 902; 354)	4168 (2 470 200; 169)	1.88 (1.74 to 2.03)
Basal cell cancer	1587 (203 215; 781)	11 073 (2 084 293; 531)	1.22 (1.07 to 1.41)

*Adjusted for age, sex, birth year, country of birth, county of residency, and educational level.

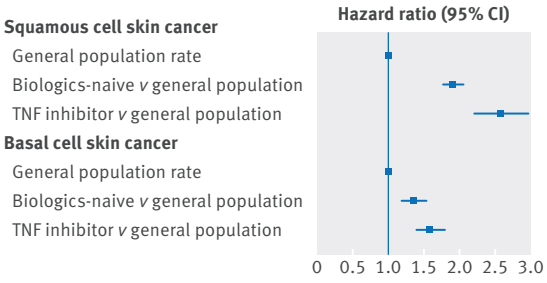

Fig 1 | Hazard ratios (95% CI) for squamous cell cancer among 46 409 biologics-naive patients with rheumatoid arthritis (RA) compared with 379 666 matched general population comparators and among 12 558 tumour necrosis factor (TNF) inhibitor treated patients with RA compared with general population comparators. Hazard ratios (95% CI) for basal cell cancer among 43 675 biologics-naive patients with RA compared with 364 584 matched general population comparators and among 8827 TNF inhibitor treated patients with RA compared with general population comparators. Hazard ratios for TNF inhibitor treated patients versus general population comparators are not discussed elsewhere in the paper but are shown here for comparison

inhibitor cohort (approximately 200/100 000 person years) and the hazard ratio for squamous cell cancer (table 3), the annual number needed to harm exceeded 1600. When analysed separately, hazard ratios for first invasive squamous cell cancer (1.30, 0.98 to 1.73) and in situ squamous cell cancer (1.28, 1.04 to 1.56) were similar (table 3).

We detected 10 second primary invasive or in situ squamous cell cancers among TNF inhibitor treated patients with a history of squamous cell cancer before the start of follow-up. Compared with 97 second primaries among patients with a history of squamous cell cancer in the biologics-naive cohort, the hazard ratio for a new invasive or in situ squamous cell cancer during follow-up was 0.99 (0.44 to 2.10) (supplementary table D).

Basal cell cancer

Biologics-naive rheumatoid arthritis versus general population

We detected 1587 first basal cell cancers in the biologics-naive rheumatoid arthritis cohort, compared with 11 073 basal cell cancers occurring in the general population comparator. The hazard ratio for basal cell cancer was 1.22 (1.07 to 1.41) (table 2 and fig 1).

TNF inhibitor treated versus biologics-naive rheumatoid arthritis

We detected 236 first basal cell cancers in the TNF inhibitor treated cohort. Compared with the biologics-naive cohort, the age and sex adjusted hazard ratio was 1.21 (1.06 to 1.41). Further adjustments for demographics and comorbidities resulted in a hazard ratio of 1.14 (0.98 to 1.33) (table 3), which did not vary appreciably across strata (table 4).

We detected 17 second primary basal cell cancers among TNF inhibitor treated patients with a history of

Table 3 | Occurrence and hazard ratios of squamous cell cancer in 12 558 TNF inhibitor treated compared with 46 409 biologics-naive Swedish RA patients, and of basal cell cancer in 8827 TNF inhibitor treated compared with 43 675 biologics-naive Swedish RA patients

	No of events (person years of follow-up; No of events/100 000 person years)		Hazard ratio	
Cancer type	TNF inhibitor treated	Biologics-naive	Adjusted for age and sex	Multivariate adjusted*
Squamous cell cancer	191 (74 541; 256)	847 (238 902; 354)	1.43 (1.22 to 1.69)	1.30 (1.10 to 1.55)
Invasive	67 (75 282; 89)	342 (241 427; 142)	1.39 (1.05 to 1.83)	1.30 (0.98 to 1.73)
In situ	141 (74 759; 189)	618 (239 984; 258)	1.42 (1.17 to 1.72)	1.28 (1.04 to 1.56)
Basal cell cancer	236 (37 080;636)	1,587 (203 215; 781)	1.21 (1.06 to 1.41)	1.14 (0.98 to 1.33)

RA=rheumatoid arthritis; TNF=tumour necrosis factor.
*Adjusted for age, sex, birth year, country of birth, county of residency, educational level, and comorbidities until start of follow-up (hospital admissions/outpatient visits for chronic obstructive pulmonary disease, ischaemic heart disease, diabetes mellitus, knee/hip joint replacement surgery, psoriatic disease. and any other diagnosis of benign skin disease except actinic keratosis; patients with diagnosis of solid organ transplantation and/or invasive malignancy before or during follow-up were considered not at risk.

basal cell cancer before the start of follow-up, compared with 41 second primaries among patients with a history of basal cell cancer in the biologics-naive cohort. The hazard ratio for a new invasive or in situ basal cell cancer during follow-up was 1.19 (0.67 to 2.15) (supplementary table D).

Sensitivity analyses

Comparing patients starting TNF inhibitors with those naive to biologics, we found no major difference in hazard ratios for in invasive or in situ squamous cell cancer of the head/face (1.33, 1.07 to 1.64) compared with the rest of the body (1.19, 0.93 to 1.54); we also found no difference for basal cell cancers (1.14, 0.94 to 1.38, versus 1.17, 0.95 to 1.47). Relative risks of squamous cell cancer comparing the TNF inhibitor cohort with three different subsets of the biologics-naive cohort ("switchers," "stable on methotrexate," and "incident rheumatoid arthritis") resulted in hazard ratios between 1.27 and 1.59 (supplementary table E).

Adjusting for use of oral corticosteroids, ciclosporin, cyclophosphamide, and/or azathioprine during follow-up among patients starting follow-up on 1 July 2005 at the earliest did not have any significant effect on the hazard ratios for either first squamous cell cancer (4815 TNF inhibitor versus 23 139 biologics-naive) or first basal cell cancer (4782 TNF inhibitor versus 22 981 biologics-naive) (supplementary table F).

Discussion

With more than 1000 squamous cell cancers and 1800 basal cell cancers, our findings represent the largest study of NMSC in rheumatoid arthritis to date and the first to investigate in situ and invasive squamous cell cancer separately. For patients with rheumatoid arthritis naive to biologic drugs, we found a 20% increased risk of basal cell cancer and a near doubled risk of squamous cell cancer, compared with the general population. For rheumatoid arthritis patients treated with TNF inhibitors compared with those naive to biologics, we found a moderately increased risk of basal cell cancer that was not significant after adjustments for demographics and comorbidities and a 30% increased risk of squamous cell cancer with no difference between in situ

Table 4 | Number of invasive or in situ squamous cell cancers and hazard ratios in 12 558 TNF inhibitor treated (1998-2012) versus 46 409 biologics-naive RA patients, and number of basal cell cancer and hazard ratio in 8827 TNF inhibitor treated (2004-12) RA versus 43 675 biologics-naive RA patients

	Squamous cell cancer		Basal cell cancer	
Characteristics	TNF inhibitor treated: No of events (individuals in strata)	Hazard ratio* (95% CI)	TNF inhibitor treated: No of events (individuals in strata)	Hazard ratio (95% CI)
Overall	191 (12 558)	1.43 (1.22 to 1.69)	236 (8827)	1.14 (0.98 to 1.33)
Female	140 (9473)	1.52 (1.25 to 1.84)	172 (6601)	1.06 (0.89 to 1.27)
Male	51 (3085)	1.26 (0.92 to 1.70)	64 (2226)	1.38 (1.03 to 1.86)
Age at start of TNF inhibitor†:				
16-49 years	12 (3944)	2.74 (1.10 to 6.82)	20 (2787)	1.34 (0.78 to 2.29)
50-74 years	142 (7963)	1.42 (1.17 to 1.73)	174 (5566)	1.15 (0.96 to 1.36)
≥75 years	37 (650)	1.36 (0.97 to 1.91)	42 (474)	1.40 (1.03 to 1.99)
Time since start of TNF inhibitor‡:				
≤6 months	16 (522)	1.93 (1.01 to 3.53)	26 (496)	0.97 (0.61 to 1.58)
6.1 months-5 years	100 (5258)	1.51 (1.21 to 1.88)	140 (4937)	1.24 (1.04 to 1.48)
>5 years	75 (6778)	1.27 (0.97 to 1.65)	70 (3394)	1.12 (0.78 to 1.60)
Start year of TNF inhibitor:				
1998-2003	89 (3576)	1.27 (1.01 to 1.61)	–	–
2004-12	102 (8893)	1.60 (1.30 to 1.98)	236 (8827)	1.13 (0.97 to 1.32)

RA=rheumatoid arthritis; TNF=tumour necrosis factor.
*TNF inhibitor treated versus biologic-naive; adjusted for age and sex.
†Test for heterogeneity across strata, P=0.79.
‡Test for heterogeneity across strata, P=0.34.

and invasive lesions. People with a history of the outcome did not seem to be at particularly elevated risk of new skin malignancies.

Neither analyses in which the TNF inhibitor treated cohort was restricted to ongoing treatment for at least 180 days after starting treatment nor those using an "as treated" definition of exposure altered the hazard ratios for the primary outcomes significantly (data not shown). We observed some confounding by comorbidity and contextual factors, but neither oral corticosteroids nor other immunosuppressive drugs were confounders for the risk of squamous cell or basal cell cancer when analysed in a subcohort of TNF inhibitor treated and biologics-naive patients.

In the clinical context in which TNF inhibitor treatment is started, the chance of detecting any prevalent cancer may be heightened. This could in theory deplete the TNF inhibitor cohort of NMSC. On the other hand, more frequent healthcare visits after starting treatment could introduce surveillance or detection bias leading to increased risk estimates. Analyses stratified on time since start of treatment resulted in the highest point estimates of increased risk for squamous cell cancer during the first years after starting TNF inhibitor treatment, rather than later. If this reflects detection bias it should be agnostic to histology, but we did not find any similar "early" increase in risk for basal cell cancer. Alternatively, blockade of TNF might specifically interfere with squamous cell cancers, making them more easily recognisable and diagnosed soon after the start of treatment. Importantly, we detected no increased risk of squamous cell or basal cell cancer associated with TNF inhibitor treatment among people with a history of the outcome. This may be due to a selection of low risk (with regards to risk of a second NMSC) patients to receive TNF inhibitor treatment in spite of a previous squamous cell cancer. We found no indication of differential risks for different tumour locations.

Comparison with other studies

Our findings with regards to biologics-naive rheumatoid arthritis are in concert with studies of rheumatoid arthritis populations from the 1980s and 90s, as well as more recent investigations.[8-12 16 25] These previous studies (supplementary table A) indicate a 20-80% increased risk of NMSC in biologics-naive rheumatoid arthritis, compared with the general population. Notably, the reporting of NMSC was not mandatory in several of the study settings,[10 16 26] leading to lower incidence rates and potentially differential reporting between rheumatoid arthritis and the general population. We were able to study squamous cell and basal cell cancer separately and found that both types of cancers were more common among biologics-naive rheumatoid arthritis patients than in the general population, but also that the level of increase in risk was more pronounced for squamous cell cancer.

A meta-analysis including data from randomised controlled trials in 8800 patients with rheumatoid arthritis detected no increased risk of NMSC (not further specified) with TNF inhibitor treatment.[27] On the other hand, in a meta-analysis of 74 randomised clinical trials including more than 22 000 patients across a range of indications, the risk of NMSC (which could be separated neither into squamous cell and basal cell cancer nor by stage) associated with TNF inhibitors was doubled (hazard ratio 2.02, 1.11 to 3.95) compared with the placebo arms.[15] The median follow-up of the included trials was four months. The finding of a distinct risk of NMSC early after starting treatment is reflected in our study, at least for squamous cell cancer.

A meta-analysis of observational studies indicated an increase in risk of NMSC of a similar level of magnitude (hazard ratio 1.45, 1.15 to 1.76) to that in our study.[17] Our findings are also partly compatible with data from the US National Data Bank for Rheumatic Diseases (NDB) and one US study using administrative data,[10 16 18] reporting relative risks of NMSC in TNF inhibitor treated RA in the range of 1.2 to 1.5. The incidence rates of NMSC combined was substantially lower than in our study, presumably related to the different methods of case ascertainment used, and squamous cell and basal cell cancer were not studied separately. By contrast, studies in European settings have not confirmed any increased risk of NMSC associated with TNF inhibitor treatment in rheumatoid arthritis. The Danish biologics register reported a hazard ratio of 1.10 (0.69 to 1.76) based on 42 cases of NMSC.[12] As squamous cell and basal cell cancer were used as a composite endpoint, and as basal cell cancer is three to six times more common than squamous cell cancer,[28] this may have diluted any true increase in risk of squamous cell cancer, if it existed. (For comparison, we considered squamous cell and basal cell cancer as a composite endpoint in our material, which yielded a fully adjusted hazard ratio of 1.21 (1.07 to 1.38) and an annual NNH of around 700). A recent study from the British biologics register investigated squamous cell and basal cell cancer separately and reported no increased risk of the latter with TNF inhibitor treatment.[25] Limited power, however, precluded firm conclusions about the risk of squamous cell cancer (23 cases among TNF inhibitor treated and four among biologics-naive patients; hazard ratio 1.16, 0.35 to 3.84).

In our study, patients treated with TNF inhibitors were at increased risk of squamous cell cancer but not of basal cell cancer, which could be compatible with the differing causes of the two cancers.[3] Immunosuppressive states such as occur in AIDS or after solid organ transplantation seem to be particularly associated with the development squamous cell cancer but only to a lesser extent with the development of basal cell cancer.[3 4] Other risk factors, such as human papilloma virus and smoking,[29] are validated risk factors for squamous cell cancer but seem less important for basal cell cancer.

Strengths and limitations of study

We included the vast majority of biologics-naive and TNF inhibitor treated rheumatoid arthritis patients in Sweden during the study period. Linkage to national health and census registers with high coverage minimised losses to follow-up and enabled us to use

prospectively collected information on covariates and outcomes. Reporting of skin cancer to the national cancer register is mandatory and semi-automated from pathology departments. We adjusted for several potential confounders such as age, sex, country of origin, residential area, benign skin disease, and other comorbidities. We did a series of stratified analyses and sensitivity analyses to explore the robustness of our findings by using different definitions of the study population and of the outcomes.

Our study has some limitations. Basal cell cancer has been reported to the cancer register nationwide only since 2004, which limited our assessment of this cancer (before and after follow-up) to patients starting TNF inhibitor treatment from 2004 onwards. Furthermore, data on duration of rheumatoid arthritis, health assessment questionnaire (HAQ) score, and disease activity score 28 (DAS28) were primarily available for the TNF inhibitor treated patients at time of starting treatment and unavailable for the comparator groups. We explored the relevance of these potential factors by using three groups of biologics-naive rheumatoid arthritis patients defined by modifications in disease modifying anti-rheumatic drug treatment as comparators. These sensitivity analyses did not indicate that the choice of comparator had any major effect on the strength of the observed association and indirectly suggested that disease activity and similar factors may not be driving the association. However, we cannot exclude the possibility of residual or unmeasured confounding, particularly that related to accumulated burden of severity of rheumatoid arthritis or past treatment exposures not captured within the timeframes of our study.

Smoking is a confirmed risk factor for squamous cell cancer,[29] but we lacked information of smoking status. However, previous assessments in the same population of Swedish rheumatoid arthritis patients indicate equal proportions of current/former smokers among TNF inhibitor treated and biologics-naive patients,[30] so we consider smoking not to be a likely confounder in our study. This is supported by the fact that adjustment for chronic obstructive pulmonary disease as a proxy of smoking changed the main result by less than 10%. We lacked information on sun exposure but adjusted the analyses for residential area as a proxy. Finally, the estimation of numbers needed to harm (NNH) is based on the underlying assumption that every year of follow-up among the TNF inhibitor treated patients equals a constant exposure during that time period (the "ever exposed" approach). As this measure is constructed of an absolute risk difference, it varies substantially according to the crude incidence rate (and hence, in the case of NMSC, with the age) of the population in the equation, and the NNH presented should be regarded as indicative of the order of magnitude rather than an exact figure.

Conclusion and clinical relevance

In conclusion, we noted a small to moderate increase in risk for basal cell cancer in rheumatoid arthritis patients naive to biologic agents but no further effect of TNF inhibitor treatment. For squamous cell cancer, we noted a near doubled risk in biologics-naive rheumatoid arthritis patients and a further 30% increase in risk in patients treated with TNF inhibitors. Under the assumption that the association with TNF inhibitor reflects causality, more than 1600 years of TNF inhibitor treatment experience would be needed to cause one additional squamous cell cancer. We noted no increasing relative risks with longer time on treatment, nor any particular increase in patients with a history of a squamous cell cancer.

Although heightened clinical vigilance for skin malignancies may be advisable, our findings imply that, whatever the mechanism, most of the increase in risk for squamous cell and basal cell cancer in rheumatoid arthritis patients treated with TNF inhibitors comes from factors other than that treatment.

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Contributors: PR, JFS, and JA were responsible for study concept and design. PR, JFS, JA, and the ARTIS Study Group acquired the data. PR, JFS, and JA analysed and interpreted the data and drafted the manuscript. All authors critically revised the manuscript for important intellectual content. PR and JA did the statistical analyses. JA obtained funding. PR and JA provided administrative, technical, or material support. PR and JA supervised the study. All authors, external and internal, had full access to all of the data. PR is the guarantor.

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Data sharing: no additional data available

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Supplementary figure and tables