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CONCISE REPORT

Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritides – a follow-up study from the DANBIO Registry

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ABSTRACT

Objectives To investigate the incidence of cancer in arthritis patients treated with or without TNFα inhibitors (TNF-I).

Methods Arthritis patients from the DANBIO database were followed-up for cancer in the Danish Cancer Registry during 2000–2008.

Results Hazard ratio for cancer overall was 1.02 (95% confidence interval (CI) 0.80-1.30) in 3347 TNF-I-treated RA patients compared to non-treated. Excess among TNF-I-treated was found for colon cancer (HR 3.52 (95% CI 1.11-11.15), whereas 6 and 0 ovarian cancer cases were observed in treated and non-treated patients, respectively. Compared to the general population, TNF-I-treated RA patients had increased risk for cancer overall, cancer in lymphatic-haematopoietic tissue and non-melanoma skin cancer, while non-RA patients had no increase in overall cancer risk.

Conclusions Our results suggest that TNF-I therapy in routine care is not associated with an overall excess of cancer in arthritis patients, but observed increased risks of colon and ovarian cancer need further investigation.

INTRODUCTION

Treatment with TNFα inhibitors (TNF-I) is widely used in inflammatory rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PSA).

After more than 10 years of widespread use, it is still debated whether treatment with TNF-I agents is associated with an increase in cancer incidence,[1–12] and additional observational studies with long-term follow-up, detailed drug history and independent registration of specific cancer cases are needed. The aim of the present study was to investigate the risk of cancer among TNF-I-treated patients by linking the national Danish DANBIO database of arthritis patients with the Danish Cancer Registry.

MATERIALS AND METHODS

DANBIO

Since 2000 Danish rheumatologists have voluntarily registered patients treated with TNF-I agents in the DANBIO database,[13] and in 2006 reporting became compulsory. Coverage for TNF-I-treated patients is steadily greater than 90%. Since 2000, an increasing number of both prevalent and newly diagnosed non-TNF-I-treated arthritis patients from rheumatology departments have also been registered in DANBIO. At the beginning reporting occurred on a voluntary basis but since 2006 the departments have been committed to register all newly diagnosed or newly referred RA patients. In 2006–7 a DANBIO-initiated cross-sectional study involving 11 of 26 Danish outpatient departments of rheumatology contributed with the registration of 3704 RA patients in DANBIO, among these 2977 were TNF-I naive.[14]

For details of the Central Population Register, the Danish Cancer Registry and statistical analysis, see supplementary material (available online only).

Cohort identification and follow-up

A total of 10 495 patients registered in DANBIO between January 2000 and December 2008 was included. Among these patients, seven patients with systemic lupus erythematosus and 52 patients with a missing diagnosis were excluded. The remaining 10 436 patients were linked to the Central Population Register (information on dates of death or emigration) and to the Danish Cancer Registry (identification of all cancer cases to 2008), and 740 patients with a cancer diagnosis before first registration in DANBIO were subsequently excluded, leaving 9696 patients with arthritis for analysis. Among these, 5345 started TNF-I therapy between January 2000 and the end of 2008, while 4351 patients had never been treated with anti-TNFα (table 1).

The cohort was followed from first registration in DANBIO until the date of first cancer diagnosis, death, emigration or the end of 2008, whichever came first. For patients who did not start treatment with TNF-I at the date of the first registration in DANBIO, the exposure status changed from never exposed to ever exposed at the date of the start of first TNF-I treatment (n=1475).

Table 1 Number of arthritis patients in DANBIO and characteristics of RA patients at first registration according to ever and never treatment with TNF-I

	Ever treated with TNF-I*	Never-treated with TNF-I
No of arthritis patients		
All combined	5345	4351
RA	3347	3812
Ankylosing spondylitis	861	136
Psoriatic arthritis	656	224
Other arthritides	481	179
Characteristics of RA patients at start of follow-up		
Mean age at start of follow-up, years (range)	54.3 (15–87)	61.2 (15–92)
Mean age at diagnosis, years	44.9	51.8
No of men (%)	902 (27)	998 (26)
Calendar year of inclusion		
2000–1	379	92
2002–3	561	46
2004–5	948	62
2006–7	1069	2807
2008	390	805
No of IgM RF seropositive† (%)	2411 (80)	2593 (74)
Mean disease duration, years (range)	10.7 (0–59)	8.9 (0–68)
Proportion with disease duration <2 years	18.7%	31.6%
Mean no of tender joints of 28 count† (range)	9.6 (0–28)	4.1 (0–28)
Mean no of swollen joints of 28 count† (range)	7.4 (0–28)	2.8 (0–28)
Mean HAQ score† (range)	1.3 (0–9.6)	0.7 (0–3.0)
Mean CRP, mg/l† (range)	27.0 (0–363)	15.2 (0–232)
Mean DAS28† (range)	5.1 (1.2–8.5)	3.5 (1.0–8.4)

*The number of rheumatoid arthriris (RA) patients ever treated with adalimumab was 1529 (46%), etanercept 1488 (44%) and infliximab 1617 (48%).
†Patients with missing values were not included. The percentage of patients with missing values was as follows (ever tumour necrosis factor α inhibitor (TNF-I) treated, never-treated): number of IgM rheumatoid factor (RF) seropositive (9.7%, 8.4%), number of tender joints (7.3%, 3.5%), number of swollen joints (5.7%, 3.3%), health assessment questionnaire (HAQ) score (18.1%, 16.6%), C-reactive protein (CRP) (6.4%, 12.3%), disease activity score in 28 joints (DAS28) (20.4%, 29.4%).

RESULTS

The DANBIO arthritis cohort experienced 24,811 person-years of observation, that is, 15,592 person-years accumulated after TNF-I treatment and 9,219 person-years accumulated in non-treated (never-treated patients and before TNF-I treatment). The mean follow-up time was 2.9 years in TNF-I-treated patients and 2.1 years in non-treated patients.

Overall, we observed 280 cancers in the total DANBIO RA cohort, with 222.7 expected from the general population, yielding a standardised incidence ratio (SIR) of 1.26 (95% CI 1.12 to 1.41). An increased SIR was observed for non-Hodgkin lymphoma 2.06 (95% CI 1.11 to 3.83), Hodgkin lymphoma 4.81 (95% CI 1.20 to 19.2), non-melanoma skin cancer 1.84 (95% 1.47 to 2.31) and lung cancer 1.47 (95% CI 1.07 to 2.03). No increased risk was observed for colon cancer 1.08 (95% CI 0.67 to 1.74).

No increase in the overall cancer risk was observed among RA patients treated with TNF-I compared to non-treated patients, whereas a significantly increased risk for all cancers was observed when comparing TNF-I-treated RA patients with the general population (table 2).

The same pattern with no increase in risk among TNF-I-treated patients relative to non-treated patients, but an increase in risk relative to the general population was seen for non-melanoma skin cancer and cancer in lymphatic and haematopoietic tissue (table 2). No increased risk of non-Hodgkin and Hodgkin lymphoma combined was observed among RA patients receiving TNF-I therapy when compared to patients not receiving therapy 0.92 (95% CI 0.29 to 2.92), while an increased SIR of 2.42 (95% CI 1.15 to 5.07) was observed when compared to the general population.

A significantly increased risk of colon cancer (HR 3.52, 95% CI 1.11 to 11.15) was observed in TNF-I-treated RA patients compared to non-treated patients, while a non-significantly increased risk was seen compared to the general population (SIR 1.61, 95% CI 0.93 to 2.77), based on 13 observed and 8.1 expected cases. Among non-treated patients the SIR of colon cancer was 0.53 (95% CI 0.20 to 1.40). Six cases of ovarian cancer were seen in TNF-I-treated RA patients, whereas no cases were observed in non-treated patients. The risk of ovarian cancer was non-significantly increased among those treated in comparison with the general female population (SIR 2.08, 95% CI 0.94 to 4.64).

No significant increase in the risk for all cancer sites combined was observed in any of the non-RA arthritis groups compared to the general population.

Various adjustments for disease activity and stratified analyses in TNF-I-treated RA patients compared to non-treated patients did not reveal increased risks for overall cancer (table 3).

DISCUSSION

The strengths of our study include high coverage of biologically treated patients (>90%) as well as a high validity of the RA, AS and PSA diagnoses in the DANBIO Registry. The registration in DANBIO was independent of registration in the cancer registry. We had complete follow-up and had the possibility to compare the cancer risks in TNF-I-treated RA patients with non-treated patients recruited from the same rheumatology departments to minimise confounding, even though confounding from factors influencing treatment decisions such as comorbidity could not be avoided. Cancer incidence in both treated and non-treated patients was also compared to that of the general population of Denmark. In clinical practice in Denmark, previous or actual cancer disease is generally a contraindication for TNF-I treatment. Therefore, to avoid differences in the prevalence of cancer among treated and non-treated patients, we excluded all patients with a previous cancer diagnosis. The cancer incidence during the first year after initiating TNF-I treatment is most likely to be influenced by selection bias, but exclusion of the first year after initiating TNF-I treatment did not change the overall risk of cancer.

We found a moderately increased overall cancer risk in RA compared to the general population. However, there was no increase in overall cancer risk among RA patients treated with TNF-I agents compared to RA non-treated patients, which is in line with other observational studies,[3 4 6 12] and a recent meta-analysis.[5] A meta-analysis of selected randomised trials of RA patients in TNF-I treatment with adalimumab or infliximab reported a three times increased risk of cancer during short-term follow-up,[1] which was not confirmed in a recent meta-analysis.[2] Also in support of no effect of TNF-I on overall cancer incidence, we found no evidence of an increase in overall risk by the cumulative duration of anti-TNF therapy, and risks did not vary by sex or age at the start of treatment.

In accordance with our findings, several studies have demonstrated a two to fourfold increased risk of malignant lymphomas in RA patients compared to the general population.[7–9 12 15] The incidence of lymphomas was the same in our TNF-I-treated and non-treated RA patients, based on small numbers. Our results

Table 2 Risk of cancer after treatment with TNF-I agents among patients with RA and patients with other types of arthritides

Site*	No of cancers treated with TNF-I		TNF-I treated vs non-treated	TNF-I treated vs general population	Non-treated vs general population
	Yes	No	HR† (95% CI)	SIR‡ (95% CI)	SIR‡ (95% CI)
All cancer sites combined					
RA patients	152	128	1.02 (0.80 to 1.30)	1.27 (1.08 to 1.49)	1.25 (1.05 to 1.48)
All non-RA	28		–	1.14 (0.79 to 1.65)	–
AS	8		–	0.82 (0.41 to 1.64)	–
PSA	12		–	1.16 (0.66 to 2.04)	–
Other arthritides	8		–	1.80 (0.90 to 3.60)	–
Specific sites for RA patients					
Digestive organs	23	18	1.12 (0.60 to 2.11)	1.17 (0.78 to 1.76)	1.01 (0.64 to 1.60)
Colon	13	4	3.52 (1.11 to 11.15)	1.61 (0.93 to 2.77)	0.53 (0.20 to 1.40)
Rectum	2	6	0.28 (0.06 to 1.43)	0.45 (0.11 to 1.79)	1.53 (0.69 to 3.42)
Pancreas	3	3	0.72 (0.14 to 3.62)	1.09 (0.35 to 3.38)	1.23 (0.40 to 3.80)
Respiratory and intrathoracic organs	20	21	0.83 (0.45 to 1.55)	1.32 (0.85 to 2.05)	1.61 (1.05 to 2.47)
Lung	18	20	0.78 (0.41 to 1.49)	1.30 (0.82 to 2.07)	1.67 (1.08 to 2.59)
Skin	48	37	1.14 (0.73 to 1.78)	1.87 (1.41 to 2.48)	1.66 (1.20 to 2.29)
Melanoma of skin	6	3	1.54 (0.37 to 6.34)	1.57 (0.70 to 3.49)	1.00 (0.32 to 3.11)
Non-melanoma skin	42	34	1.10 (0.69 to 1.76)	1.92 (1.42 to 2.59)	1.76 (1.26 to 2.46)
Breast	14	14	0.73 (0.35 to 1.55)	0.69 (0.41 to 1.16)	0.89 (0.53 to 1.51)
Female genital organs	9	2	3.92 (0.84 to 18.41)	1.03 (0.53 to 1.97)	0.30 (0.07 to 1.19)
Corpus uteri	2	2	0.79 (0.11 to 5.58)	0.53 (0.13 to 2.13)	0.69 (0.17 to 2.75)
Ovary	6	0	–	2.08 (0.94 to 4.64)	–
Male genital organs	6	10	0.64 (0.22 to 1.83)	0.89 (0.40 to 1.98)	1.42 (0.76 to 2.63)
Prostate	6	10	0.64 (0.22 to 1.83)	0.94 (0.42 to 2.09)	1.47 (0.79 to 2.72)
Urinary tract	9	7	1.12 (0.41 to 3.09)	1.31 (0.68 to 2.52)	1.12 (0.54 to 2.36)
Urinary bladder	5	5	0.77 (0.22 to 2.75)	1.09 (0.45 to 2.61)	1.16 (0.48 to 2.78)
Eye, brain, central nervous system	1	6	0.20 (0.02 to 1.73)	0.26 (0.04 to 1.85)	2.01 (0.90 to 4.47)
Lymphatic and haematopoietic tissue	14	9	1.25 (0.53 to 2.92)	2.24 (1.33 to 3.79)	1.66 (0.86 to 3.19)
Hodgkin lymphoma	2	0	–	8.27 (2.07 to 33.1)	–
Non-Hodgkin lymphoma	5	5	0.63 (0.18 to 2.20)	1.88 (0.78 to 4.53)	2.27 (0.94 to 5.45)
Multiple myeloma	2	2	0.90 (0.13 to 6.44)	1.68 (0.42 to 6.74)	1.86 (0.47 to 7.45)
Lymphatic leukaemia	3	1	3.18 (0.33 to 31.08)	2.42 (0.78 to 7.49)	0.87 (0.12 to 6.19)
Ill-defined and unspecified cancer	4	2	1.51 (0.27 to 8.58)	1.31 (0.49 to 3.48)	0.68 (0.17 to 2.72)

*Only specific cancer sites with more than three cases in tumour necrosis factor α inhibitor (TNF-I)-treated and non-treated combined are shown. Results for Hodgkin lymphoma are also presented.
†Estimated by HR ratios using Cox proportional hazard models with age as the underlying time scale and with further adjustment for sex and calendar time (2000–4, 2005–8). HR was not calculated for anlylosing spondylitis (AS), psoriatric arthritis (PSA) or other arthritides patients because of the small number of patients and short follow-up time in the non-TNF-I-treated group.
‡Estimated by standardised incidence ratios (SIR), ie, the ratio between observed and expected cancer cases during follow-up. The expected number of cancer cases was calculated by multiplying the number of person-years experienced by the cohort members with sex and 5-year age and calendar-specific incidence rates for first cancers in the general population in Denmark.
RA, rheumatoid arthritis.

are in agreement with the conclusions of earlier studies[3 5 7 8 10 12] except a French study.[9]

We found an increased incidence of non-melanoma skin cancer combining squamous and basal cell carcinomas in our RA cohort compared to the general population, which is in accordance with a previous Danish study of hospitalised RA patients[15] and studies of other immunosuppressive cohorts.[16 17] However, we found that the incidence of non-melanoma skin cancer was similar for TNF-I-treated and non-treated RA patients. A recently published British study reported that skin cancer was increased among RA patients, but found no evidence that TNF-I therapy exacerbated the risk of basal cell or squamous cell carcinomas further.[18]

An increased risk of colon and ovarian cancer was observed in RA patients treated with TNF-I agents compared to non-treated patients. Evidence from previous studies concerning these cancers is sparse. Wolfe and Michaud[3] reported risks specifically for colon and ovarian cancer when comparing TNF-I-treated with untreated patients and the risks were not significantly elevated. Surveillance bias does not seem an obvious explanation, because increased surveillance would have been expected to result in a general increase in cancer incidence at many sites. One may hypothesise that a higher use of non-steroidal anti-inflammatory drugs or aspirin in the disease-modifying antirheumatic drug-treated group and a more sedentary lifestyle in the TNF-I-treated group due to higher disability, as indicated by the health assessment questionnaire or dietary factors,[19 20] may affect the incidence rate of colon cancer. Larger studies are needed to determine whether the increased risks of colon and ovarian cancer were chance findings in our study.

In conclusion, we found no excess of overall cancer associated with TNF-I therapy in RA patients in routine care. However, increased risks of colon and ovary cancer were found and need further investigation. We did not find an increase in the overall cancer risk in TNF-I-treated AS, PSA and other arthritides patients compared to the general population.

Table 3 Risk of overall cancer after treatment with TNF-I agents among patients with RA by adjustment for various measures of disease activity at enrolment, gender, time since initiation, cumulative duration of treatment and age at treatment start

Variable	No of cancers among treated†	TNF-I treated versus non-treated HR‡ (95% CI)	p Value*
Ever TNF-I treatment			
Overall effect	152	1.02 (0.80 to 1.30)	
Plus adjustment for HAQ§		0.95 (0.74 to 1.22)	
Plus adjustment for CRP§		0.99 (0.77 to 1.26)	
Plus adjustment for DAS28§		0.96 (0.74 to 1.24)	
Men	48	0.83 (0.55 to 1.26)	p=0.24
Women	104	1.13 (0.83 to 1.53)	
Time since treatment initiation, years			
<1	41	1.04 (0.72 to 1.50)	
1–4	97	1.03 (0.79 to 1.35)	p=0.86
5+	14	0.88 (0.51 to 1.54)	
1+	111	1.01 (0.78 to 1.30)	
Cumulative duration of treatment, years			
<1	43	1.04 (0.73 to 1.48)	
1–2	39	1.19 (0.83 to 1.71)	p=0.69
2–3	29	1.09 (0.72 to 1.63)	
4+	41	0.86 (0.60 to 1.22)	
Age at treatment start, years			
<50	12	0.83 (0.38 to 1.82)	
50–64	69	0.97 (0.68 to 1.37)	p=0.76
≥65	71	1.10 (0.80 to 1.50)	

*p Values for homogeneity test based on Wald statistics.
†There were 128 cancer cases observed among non-tumour necrosis factor α inhibitor (TNF-I)-treated patients.
‡HR ratios estimated using Cox proportional hazard models with age as the underlying time scale and with further adjustment for sex and calendar time (2000–4, 2005–8).
§Adjustment for high disease activity at first visit (health assessment questionnaire (HAQ) ≥2; C-reactive protein (CRP) ≥30 mg/l; disease activity score in 28 joints (DAS28) ≥5.1). Similar results were found after adjustment for the same disease activity measures at the latest visit or at any time.
RA, rheumatoid arthritis.

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Contributors LD contributed to the conception and design, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content and final approval of the version to be published. LM and MLH contributed to the conception and design and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published. ARA, PB, UEP, TJE, THH, DVJ, LL, HML, AGRL, HN, EO, CR, AS and UT contributed to the conception and design, revising the article critically for important intellectual content and final approval of the version to be published.

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Correction notice This article has been corrected since it was published online first. Affiliation 3 has been altered.

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Notes