

## EXTENDED REPORT

# Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas

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**Objective:** To determine whether TNF blockers increase tumour risk in patients with RA.

**Material and methods:** The South Swedish Arthritis Treatment Group register (SSATG) comprises over 90% of anti-TNF treated patients with RA in the area. 757 patients treated with etanercept or infliximab included between 1 February 1999 and 31 December 2002 were identified. 800 patients with conventional antirheumatic treatment in a community based cohort served as a comparison cohort. Tumours and deaths were identified in the cancer registry and population census registers. Patients were followed up from initiation of anti-TNF treatment or 1 July 1997 for the comparison group, until death or 31 December 2002.

**Results:** In the anti-TNF group, 16 tumours (5 lymphomas) were identified in 1603 person-years at risk, and in the comparison group 69 tumours (2 lymphomas) in 3948 person-years. Standardised incidence ratios (SIRs) for total tumour relative risk for the anti-TNF group and the comparison group were 1.1 (95% confidence interval (CI) 0.6 to 1.8) and 1.4 (95% CI 1.1 to 1.8), respectively. The lymphoma relative risk (RR) was 11.5 (95% CI 3.7 to 26.9) and 1.3 (95% CI 0.2 to 4.5), respectively. The total tumour RR excluding lymphoma was 0.79 (95% CI 0.4 to 1.42) and 1.39 (95% CI 1.08 to 1.76), respectively. Proportional hazard analysis for lymphomas yielded RR 4.9 (95% CI 0.9 to 26.2) in anti-TNF treated versus untreated patients.

**Conclusion:** Community based patients with RA treated conventionally had an increased overall tumour risk compared with the background population. A possible additional increased risk for lymphoma associated with TNF blockers was based on few cases and needs confirmation.

Ever since the introduction of the new biological treatments for Crohn's disease and rheumatoid arthritis (RA) there have been concerns about a possible tumour promoting effect. Tumour necrosis factor (TNF) and interleukin 1 have a documented tumour reducing capacity,<sup>1,2</sup> and treatment with anti-TNF drugs, such as the antibodies infliximab or adalimumab or the soluble TNF receptor etanercept as well as the anti-interleukin 1 antibody anakinra, might thus theoretically promote formation of tumours.

In both Crohn's disease<sup>3,4</sup> and RA<sup>5–11</sup> increased risks of developing malignancies in the lymphoid tissues have been reported. In RA other haematopoietic malignancies are also increasingly reported.<sup>5,10,12,13</sup> Especially in RA, these increases have been attributed to persistent inflammatory disease activity,<sup>14</sup> and recently a more detailed analysis has shown that large B cell neoplasms predominate among these RA related lymphomas.<sup>15</sup> Alkylating drugs have been used for RA treatment,<sup>16</sup> and have been reported to be associated with malignancies.<sup>17,18</sup> These drugs are nowadays mainly used to treat life threatening complications such as severe vasculitis or amyloidosis. Also, other antirheumatic treatments, such as methotrexate and azathioprine, have been implicated as possible tumour promoters in RA, although the evidence is conflicting.<sup>19–22</sup>

Although clinical trials of anti-TNF drugs have not reported an increased incidence of malignant tumours compared with the expected levels, the selection of patients

for such trials may exclude patients more prone to develop such complications. Also, introduction of these treatments to new diagnostic groups, where the background tumour prevalence is not well established, poses problems when evaluating the incidence of tumours in anti-TNF treated cohorts. Recently there have been reports and specific Food and Drug Administration hearings of a possibly increased incidence of lymphomas/leukaemias in patients treated with anti-TNF drugs.<sup>23</sup> However, both the lack of a control population and the shortcomings of the official pharmacovigilance systems preclude firm conclusions at present.

In southern Sweden patients treated with anti-TNF drugs have been included in a regional register since the introduction of etanercept and infliximab in 1999.<sup>24</sup> A suitable community based comparison RA cohort from the same catchment area has been identified.<sup>25</sup> Our study aimed at estimating the incidence of malignancies including lymphomas in anti-TNF treated patients with RA and comparing it with the incidence in a cohort of community based patients with RA not treated with TNF inhibitors. Cancer diagnoses were identified by the regional Southern Swedish cancer

**Abbreviations:** DAS28, 28 joint count Disease Activity Score; DMARD, disease modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; RR, relative risk; SIR, standardised incidence ratio; SSATG, South Swedish Arthritis Treatment Group; TNF, tumour necrosis factor

**Table 1** Patient characteristics

Characteristics	Patients with anti-TNF treatment	Patients without anti-TNF treatment
Number of patients	757	800
Age at RA diagnosis (years)	42 (32–52)	49 (36–61)
RA duration at inclusion (years)	12 (5–19)	11 (4–22)
Female (%)	76	73
Age at inclusion (years)	56 (53–78)	64 (52–78)
Follow up time (years)	2.1 (1.3–3.1)	5.5 (5.3–5.5)
HAQ quartile $\geq 3$ (%)	61	41
Number of previous DMARDs	3 (2–5)	1 (0–2)
Duration of anti-TNF treatment (years)	1.7	–

Values are given as median, 25th and 75th centiles unless stated otherwise.

registry, in which all newly diagnosed malignancies are registered.

## MATERIAL AND METHODS

The South Swedish Arthritis Treatment Group (SSATG) register has been described previously.<sup>24</sup> The register covers about 1 300 000 inhabitants and includes patients treated with biological agents at eight rheumatological centres. The register data have been compared with pharmaceutical sales and the register is estimated to cover over 90% of anti-TNF treated arthritic patients in the area (Geborek *et al*, manuscript in preparation). Patients with RA treated with etanercept or infliximab in the SSATG register included between 1 February 1999 and 31 December 2002 were identified. Patient and disease characteristics, including age, sex, disease duration, the validated Swedish version of the Health Assessment Questionnaire (HAQ),<sup>26</sup> and previous disease modifying antirheumatic drug (DMARD) treatment at inclusion were retrieved from the register. More than 98% of the patients<sup>24</sup> fulfilled the 1987 American College of Rheumatology classification criteria.<sup>27</sup>

For comparison, patients with RA not treated with anti-TNF drugs were identified in a community based cohort of patients with RA in Malmö, a city from the SSATG catchment

area. Patients were recruited from the rheumatology outpatient clinic of Malmö University Hospital, which is the only hospital serving the city, and from the four rheumatologists in private practice.<sup>25</sup> In July 1997 this register comprised 1033 patients, who were sent a questionnaire which was answered by 75%. Subsequent surveys using the diagnostic index of primary care centres and questionnaires sent to other physicians in the area indicate that >90% of all patients with diagnosed RA in the city have been seen by a rheumatologist and are thus included in the register.<sup>25</sup> The 1987 American College of Rheumatology classification criteria<sup>27</sup> were fulfilled by 98% of the cohort.<sup>25</sup> Patient disease characteristics, including HAQ and previous DMARD drug treatment, were aggregated by survey in 1997. For patients not responding to the survey, information on disease onset was obtained from medical case records.

Tumours and deaths were identified in the Southern Swedish cancer registry and population census registers. The patients were followed up from the start of anti-TNF treatment or 1 July 1997 for the comparison cohort, until death or 31 December 2002.

Patients starting anti-TNF drugs were transferred from the community based Malmö cohort to the SSATG cohort. Subjects with a tumour diagnosis before inclusion were excluded from both cohorts.

The cohorts were analysed by calculating standardised incidence ratios (SIRs)—that is, the observed number of cancer cases divided by the expected number. Expected numbers were calculated by multiplying the cancer incidence in the South Swedish healthcare region (population 1.5 million) with the observed person-years at risk, stratified for sex, age, and calendar year.

Owing to the small number of observations we chose not to present each of the separate cancer diagnoses, but in groups defined as lymphomas, blood (leukaemia + myeloma), smoking related (upper gastrointestinal tract + airway + urinary tract),<sup>28</sup> and other malignancies (breast + genital + other gastrointestinal + abdominal cavity + skin + musculoskeletal).

Anti-TNF treated patients, and non-anti-TNF treated patients were further compared in a Cox proportional hazards

**Table 2** Observed (OBS), expected (EXP) number of malignancies grouped as smoking related (upper gastrointestinal tract + airway + urinary tract), blood malignancies (leukaemias + myelomas), lymphomas, and other carcinomas and sarcomas (breast + genital + other gastrointestinal + abdominal cavity + skin + musculoskeletal) for the anti-TNF treated and comparison cohort, respectively

Tumour group	OBS	EXP	SIR	95% CI	OBS SSATG
<i>Comparison cohort (n=800); person years = 3948; follow up age 0–99, male+female</i>					
Smoking related	21	8.5	2.5	1.5 to 3.8	–
Other cancers	44	38	1.2	0.8 to 1.6	–
Blood malignancies, including myeloma	2	1.8	1.1	0.1 to 4.0	–
Lymphomas	2	1.6	1.3	0.2 to 4.5	–
All malignancies	69	49.9	1.4	1.1 to 1.8	–
<i>Anti-TNF cohort (n=757); person years = 1603; follow up age 0–99, male+female</i>					
Smoking related	5*	2.3	2.2	0.7 to 5.1	4
Other cancers	6†	11.2	0.5	0.2 to 1.2	8‡
Blood malignancies including myeloma	0	0.4	0	0 to 9.2	1§
Lymphomas	5	0.4	11.5	3.7 to 26.9	5
All malignancies	16	13.4	1.1	0.6 to 1.8	18

\*One laryngeal carcinoma, diagnosed >3 years after anti-TNF withdrawal, not reported to the SSATG registry; †one prostate carcinoma and one cutaneous carcinoma, diagnosed >1 year after anti-TNF withdrawal, not reported to the SSATG registry; ‡one cervical uterine carcinoma in a patient with a previous carcinoma thus excluded from the registry search, and three basal cell carcinomas. Basal cell carcinomas are not registered in the cancer registry, but it includes all other cutaneous cancers—both melanomas and non-melanoma cancers; §moved abroad and thus excluded from the tumour registry search. Standardised incidence ratios (SIRs) and 95 per cent confidence interval (95% CI) are also shown. For the anti-TNF treated patients the numbers of malignancies reported to the SSATG register (OBS SSATG) are also shown.

**Table 3** Characteristics of anti-TNF treated patients with lymphoma/leukaemia

Treatment Initiating year	Sex	Year of birth	Rheumatic disease			Continuing DMARD at anti-TNF initiation	Therapeutic response to anti-TNF	Tumour diagnosis		
			Diagnosis	Onset	Previous DMARD*			Time of diagnosis	Anti-TNF treatment day at diagnosis	Outcome course Oct 2003
Infliximab July 2000–Nov 2000	M	1923	RA	1972	2 SSZ, ama	0	+?	Hodgkin Nov 2000	129	Fatal Nov 2000
Infliximab Apr 2000–Dec 2002	F	1926	RA, keratitis	1978	2 MTX, CYC	MTX	++	Non-Hodgkin Maxilla  Oct 2000	180	Alive
Infliximab Feb 2000–Sep 2001	F	1943	RA	1989	6 MTX, SSZ, gold IM and oral, ama	0	+++	Non-Hodgkin, B-lcc, inguinal  Sep 2001	570	Alive
Infliximab, then etanercept Mar 1999–Sep 1999, Sep 1999– Aug 2002, respectively	F	1954	RA	1989	5 MTX, SSZ ciclosp, gold IM, penicillamine	MTX	+++	MALT, lung Aug 2002	1081	Fatal Postmortem MALT diagnosis in Aug 2002
Etanercept Apr 1999–Dec 1999	F	1918	RA	1994	3 MTX, SSZ, gold IM	0	+?	Immuno- cytoma, breast Dec 1999	220	Fatal June 2000
Etanercept Apr 1999–July 2000	M	1925	RA	1976	1 MTX	MTX	++	Acute myeloid leukaemia, trisomi 8 chromosome Nov 2000	440	Moved abroad, fatal Jan 2002

\*MTX, methotrexate; SSZ, sulfasalazine; ciclosp, ciclosporin; ama, antimalarial drugs; gold IM, injectable gold; gold oral, auranofin; CYC, cyclophosphamide.

model. Hazard rates were estimated, adjusting for age, sex, and disease severity reflected by HAQ levels.

The SSATG protocol also includes a voluntary pharmacovigilance module for recording adverse events, such as tumours. To validate the reported information, the number and types of malignancies in the SSATG database were compared with those found in the regional cancer registry.

Ethical committee approval was obtained for data linkage.

## RESULTS

Of the originally identified comparison population 153 (15%) were transferred to the SSATG cohort because they started anti-TNF treatment, and 80 (8%) were excluded owing to a previous malignancy, leaving an eligible comparison population of 800 patients. In the SSATG registry, 784 patients with RA were identified. Twenty seven of these (3.4%) were excluded owing to a previous malignancy, leaving 757 eligible for analysis. Of these, 226 were treated with etanercept and 531 with infliximab, but because of the longer treatment duration for etanercept the total duration of treatments was similar (etanercept 657 years and infliximab 685 years). Table 1 shows the patient characteristics of the two cohorts.

In the anti-TNF group there were 16 tumours (five lymphomas) in 1603 person-years at risk, and in the control group 69 tumours (two lymphomas) in 3948 person-years (table 2).

The SIRs in the anti-TNF group and the control group were 1.1 (95% CI 0.6 to 1.8) and 1.4 (95% CI 1.1 to 1.8) for all tumours, and 11.5 (95% CI 3.7 to 26.9) and 1.3 (95% CI 0.2 to 4.5) for lymphomas, respectively. The total cancer risk excluding lymphomas was 0.79 (95% CI 0.4 to 1.42) among the patients treated with anti-TNF treatment and 1.39 (95% CI 1.08 to 1.76) in the comparison group. Smoking related cancers were increased in the control group with SIR 2.5

(95% CI 1.5 to 3.8) and at a similar level in the anti-TNF group with SIR 2.2 (95% CI 0.7 to 5.1). Leukaemias or myelomas were found to be no different from the background population with SIR 1.1 (95% CI 0.1 to 4.1) in the control population, and no leukaemias or myelomas were identified in the anti-TNF treated groups in the analysis (table 2).

In the proportional hazards analyses the unadjusted hazard rate for lymphoma in those anti-TNF treated patients compared with non-treated patients was 4.9 (95% CI 0.9 to 26.2,  $p = 0.07$ ), and 5.0 (95% CI 0.9 to 27.9,  $p = 0.06$ ) after HAQ adjustment.

Six patients treated with TNF blockers developed haematopoietic malignancies. Four of these had died by March 2003. Table 3 shows detailed characteristics of these patients.

All lymphomas found in the cancer registry were also identified in the SSATG pharmacovigilance database. An additional acute myeloid leukaemia in a patient treated with etanercept for 440 days before diagnosis was only registered in the SSATG database. This patient had moved abroad and was censored from the cancer registry surveillance at the date of emigration. One case of laryngeal cancer, one of prostate cancer, and one of skin cancer were only found in the regional tumour registry. Additionally, three basal cell carcinomas (this diagnosis is not included in the cancer registry) and one uterine cancer (excluded from the analysis owing to a known previous malignancy) were found in the SSATG registry. Thus, of the 16 malignancies identified in the Southern Swedish cancer registry analysis, 13 (81%) were found in the SSATG registry (table 2).

## DISCUSSION

In this study the overall incidence of cancer is not increased in anti-TNF treated patients with RA compared with the

background population. The results for overall tumour SIR in the anti-TNF treated patients compared with the control group of patients with RA must be interpreted with caution because of both the limited number of observations and the relatively short follow up period. This is emphasised by the wide overlap of confidence intervals between the anti-TNF and comparison groups. Also, the recommended active exclusion of patients with a known previous cancer from anti-TNF treatment may, to some degree, contribute to the lower incidence of cancer in this group.

The SSATG catchment area includes both rural and urban populations and represents a majority of the background population covered by the regional tumour registry. The Malmö comparison cohort is urban, but no recent tumour incidence data for Malmö are available. Annual tumour incidences from 1970 to 1997 indicate a somewhat higher overall tumour incidence, for men of around 10% and for women 2–5%, in Malmö compared with the background urban and rural population. Therefore, the presently found SIR of 1.4 in the Malmö comparison cohort suggests an increased cancer incidence compared with the background population. However, the tumour pattern shows an increase mainly for smoking related tumours in the Malmö cohort (table 2). Smoking habits have recently in several studies been implicated as a predictor and possibly also a marker of poor prognosis in RA.<sup>29–31</sup> There was also a trend towards a similar increase in smoking related tumours in the anti-TNF treated cohort (table 2), but the numbers are presently too small to draw any firm conclusions.

The increase in overall tumour frequency of 40% in the community based RA cohort found in the present study has not been reported by others,<sup>12, 13</sup> although some other studies have indicated an overall increase in the incidence of tumours of 8–10% in men.<sup>8, 10</sup> Mellekjaer *et al* reported an excess of non-haematopoietic malignancies in patients with RA of both sexes,<sup>9</sup> mainly owing to an excess of lung cancer. Other investigators have also found an increased risk of lung cancer in patients with RA,<sup>8, 10, 32, 33</sup> but this has not been confirmed in all studies.<sup>13</sup> These discrepancies may reflect differences in patient selection and in exposure to other environmental factors, including smoking. Most other studies have used inpatient registries<sup>8–10</sup> or referral centres<sup>13</sup> to identify patients with RA. Although the use of SIR adjusts for risk factors such as age, sex, and calendar year, differences in other types of exposure between cases and controls could complicate hospital based studies. In our study we used a community based outpatient cohort for identifying patients with RA, which possibly selects older and less severely affected subjects. The results should thus be more generalisable to the general overall population of patients with RA.

A possible contribution of anti-TNF treatment to the lymphoma incidence in the present study must be interpreted with caution. The anti-TNF treated cohort represents a subpopulation of patients with RA with a supposedly up to 25-fold increased lymphoma incidence due to longstanding high disease activity.<sup>14</sup> Furthermore, the patients transferred from the original RA comparison cohort to the anti-TNF group may also contribute to the lower lymphoma numbers in this group if anti-TNF treatment had not been available. Thus, some of the higher lymphoma risk in anti-TNF treated patients might be explained by a higher disease severity. In the Cox proportional hazards model the possibility of analysing disease severity properly as a confounding factor was limited because the number of cases was small. However, the current finding of an 11.5 increased lymphoma risk in anti-TNF treated patients with RA and a tendency for an increased risk when adjusting for disease severity, is disturbing and deserves further study.

Interestingly, we found that TNF blockers had been prescribed to 15% of the patients in the community based control cohort during the first 4 years after these treatments became available. This figure probably lies in the vicinity of what to expect, when relating to the 5.6% of RA outpatients eligible for such treatment using the rigid BSR-NICE criteria<sup>34</sup> when applied trans-sectionally during a restricted 2 week study period.<sup>34</sup> The Swedish Society of Rheumatology has issued similar guidelines to the BSR but with less rigid emphasis on fulfilling a particular disease activity score,<sup>34</sup> permitting also patients with a lower 28 joint count Disease Activity Score (DAS28) and use of systemic glucocorticosteroids to be considered for treatment with biological agents. When applying the BSR-NICE criteria also to patients with lower DAS28 scores, 11% were eligible for anti-TNF treatment.<sup>35</sup>

The relatively short time interval between starting anti-TNF treatment and lymphoma diagnosis in the current report might suggest both an increased awareness of such a possible relationship and more careful surveillance. However, if there is a non-random relationship between anti-TNF treatment and lymphoma diagnosis, a disturbance of the regulatory tumour controlling mechanisms of tumours already present would be suggested. An aetiological mechanism might have a somewhat longer timespan between trigger and diagnosis. However, the time interval between lymphoma diagnosis and the initiation of immunosuppression in immunocompromised patients has been reported to be short, possibly owing to viral causes of lymphomas.<sup>36</sup> As a comparison of a slumbering viral disease awakening during treatment, we have found an incidence of up to 2.0 herpes zoster infections per 100 anti-TNF treatment years in patients with RA in the SSATG registry (unpublished observation). However, the Epstein-Barr virus is seldom found in lymphoma tissues of patients with RA.<sup>7</sup> The possibility of the Epstein-Barr virus being present in lymphoma tissue in anti-TNF treated patients is currently being investigated nation wide in Sweden.

The types of lymphomas in the present report (table 3) seems to be in line with those recently reported in patients with RA,<sup>15</sup> possibly suggesting that these are more related to diagnosis than treatment, as also reported in a recent review.<sup>37</sup> This requires further study of a larger sample of lymphomas in patients with RA treated with TNF inhibitors.

The number and type of tumours reported voluntarily to the SSATG registry overlaps with the regional tumour registry in about 80% of cases. Notably, all lymphomas were found in both registries, and also one more leukaemia was found in the SSATG registry only, because the patient had moved abroad (table 2). Other discrepancies between the two registries include the exclusion of patients with a previous malignancy from the cancer registry analysis, and basal cell carcinomas presently being included in the regional tumour registry. Patients stopping anti-TNF drugs are not regularly followed up in the SSATG registry, and therefore late events such as malignant tumour manifestations may not be reported, as illustrated by the three late cases of malignancies not reported to the SSATG registry (table 2). The present study linking data from both registries overcame these errors, illustrating that the pharmacovigilance systems are complementary. However, the high degree of concordance between the two different methods of picking up this type of adverse event strengthens the validity of the SSATG registry. Moreover, in contrast with data linkage analyses, adverse event reports from the SSATG registry are regularly issued to the profession making it particularly useful in clinical practice. However, the current finding of a substantially increased risk of lymphomas in anti-TNF treated patients



indicates that careful surveillance of such patients is of major importance.

Recently, Wolfe and Michaud reported a moderate lymphoma increase in SIR of 2.9 (95% CI 1.4 to 4.5) for patients with RA treated with anti-TNF drugs, compared with an SIR of 1.7 (95% CI 0.9 to 3.2) for methotrexate treated patients with RA and an SIR of 1.0 (95% CI 0.4 to 2.5) for patients not receiving biological agents or methotrexate.<sup>38</sup> However, despite impressive patient numbers, several methodological questions can be raised about patient selection, diagnostic validity, sampling technique, as well as the limited follow up period for drug exposition as pointed out in an accompanying editorial.<sup>39</sup> A strength of the present study is the over 90% coverage in both the case and comparison cohorts leaving little room for selection bias, although some influence cannot be excluded.

In conclusion, we report that the overall incidence of cancer is not increased in patients treated with TNF blockers. We found an increased overall tumour incidence in the comparison RA cohort, mainly due to smoking related tumours. The impact of anti-TNF treatment on individual tumours, including lymphomas, should be further studied.

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