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### Risk of cancer in Turkish patients after treatment with TNF antagonists

SIR, There is conflicting evidence whether anti-TNF therapy offers an increased cancer risk in rheumatological disorders. In this study, we aimed to collect pilot data on a possible association between anti-TNF agent use and development of neoplasms among Turkish patients with various rheumatological conditions.

We conducted a nationwide survey pooling reported cases from 26 different rheumatology centers in Turkey. A total of 2199 patients (1247 females, 952 males, mean age:  $41.8 \pm 13.9$  yrs) were reported. Among those patients, 943 had AS (1027.16 patient-years) (mean age:  $37.3 \pm 10.9$  yrs), 931 RA (1145.14 patient-years) (mean age:  $49.1 \pm 12.7$  yrs), 132 PsA (mean age:  $43.6 \pm 12.5$  yrs), 127 JCA (mean age:  $23.8 \pm 10.9$  yrs) and 66 other disorders (62.14 patient-years) (mean age:  $30.9 \pm 10.3$  yrs). Nine-hundred and twenty-three patients had been treated with etanercept (1028.54 patient-years), 853 with infliximab (1014.68 patient-years) and 259 with adalimumab (223.69 patient-years). One-hundred and sixty-four patients had been treated with more than one anti-TNF agent. We used standardized incidence ratios (SIRs) as measures of relative risk were expected number were taken from a regional cancer survey conducted in the Izmir (Western Turkey) region.

Fifteen malignancies (13 solid cancers and 2 lymphoproliferative disorders) were observed (SIR = 1.26, 95% CI 0.70, 2.08). Ten patients had been treated with etanercept (SIR = 2.3, 95% CI 1.10, 4.23), three with infliximab (SIR = 0.66, 95% CI 0.14, 1.92), one with adalimumab (SIR = 0.62, 95% CI 0.02, 3.48) and one with etanercept and then adalimumab. Eleven RA patients (SIR = 1.36, 95% CI 0.68, 2.43), two AS patients (SIR = 0.66, 95% CI 0.08, 2.38) and two patients with other indications developed cancer after anti-TNF agents. Among RA patients who developed cancer, seven patients had been treated with etanercept (SIR = 2.46, 95% CI 0.99, 5.06), two with infliximab (SIR = 0.64, 95% CI 0.02, 3.56), one with adalimumab (SIR = 0.75, 95% CI 0.09, 2.72) and one with etanercept, and then switched to adalimumab (Fig. 1).

The number of studies investigating a possible association between the use of TNF alpha antagonists in RA patients and the development of cancer have been published with inconclusive results. Wolfe and Michaud [1] reported increased risk of lymphoma in RA patients compared with the general population, and the risk was greatest in patients treated with TNF- $\alpha$  antagonists. In a previous study by a regional Swedish cohort,

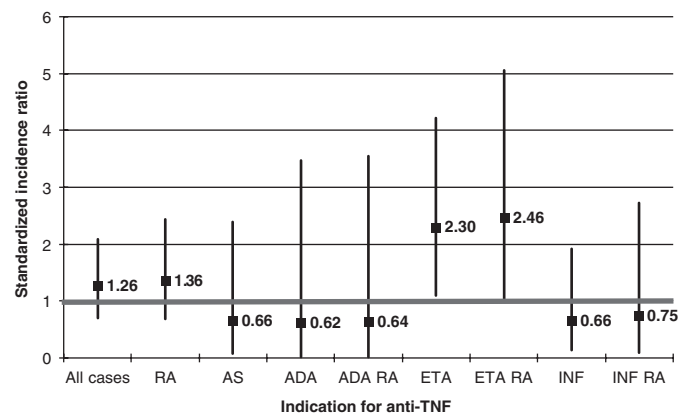


FIG. 1. SIR for total number of tumours in all, RA and AS patients treated with different anti-TNF agents. ADA: adalimumab; ETA: etanercept; INF: infliximab.

Geborek *et al*. [2] suggested that the overall incidence of cancer is not increased in patients treated with anti-TNF agents, while there may be an increased risk of lymphomas in those patients compared with RA patients treated with conventional agents. However, in the national Swedish cohort, including the data of the previous regional cohort, Askling *et al*. [3] could not find any increased risk for lymphomas in RA patients treated with TNF antagonists than other patients with RA. Setoguchi *et al*. [4] compared the risk of haematological malignancies and solid tumours in elderly RA patients from US and Canada who received biologic agents as compared with those treated with methotrexate. The authors found no significant increase in the risk of cancers in biologic agent users. Chakravarty *et al*. [5] and Wolfe and Michaud [6] demonstrated an increased risk of non-melanoma and all skin cancers in patients with RA treated with anti-TNF agents, respectively. In contrast to RA, disease-associated cancer risk has been poorly explored in AS. Recently, no overall increased risk for solid cancers or lymphomas were found in AS [7, 8].

Our nationwide survey did not show an increased risk of cancer associated with TNF antagonist use when data with etanercept, infliximab and adalimumab were considered together. On the other hand, there was an increase of cancer risk with etanercept use when these agents were considered separately and this trend was also present among RA patients taken as a separate group. There was no evidence for increased neoplasm among the AS patients.

Our study had several limitations: first, we did not re-confirm the cancer diagnoses neither clinically nor by histology. Second we did not seek information about the background risk factors for cancer, such as smoking status, or family history. Third, the comparator group for the cancer incidence represented only a limited geographic area [9]. Lastly, the total number surveyed as well as the number of cancer cases found is rather small to make robust comparisons.

Our results, which need to be interpreted in the light of shortcomings of our survey we mention above, nevertheless suggest that the risk of malignancy with the use of TNF antagonists might differ in different disease states (i.e. RA, SpAs), and with the use of different anti-TNF agents. Larger prospective collaborative studies with prolonged follow-up and more meticulous methodology will be needed in order to obtain more precise estimates.

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### Rheumatology key message

- Risk of malignancy with the use of TNF antagonists might differ in different disease states (i.e. RA, SpAs), and perhaps with the use of different anti-TNF agents.

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**APPENDIX 1.** Complete list of members of The Society for Research and Education in Rheumatology who contributed to the present study (in alphabetical order).

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### Shared familial risk factors between cancer and RA patients

SİR, Twin and family studies show that susceptibility to RA has a heritable basis, transmitted in part with some identified candidate genes [1, 2]. As RA patients are at a risk of many cancers [3], a question arises whether RA and cancer share heritable risk factors, which has not been settled. Most studies have analysed the links between RA and lymphohaemato-proliferative diseases, providing some evidence on familial aggregation [4, 5]. Family members of RA patients have not shown an overall risk of lymphoma or cancer, but childhood Hodgkin disease has been in excess and even other autoimmune conditions have been associated with Hodgkin disease [4, 5]. No data have been available on the risk of individual site-specific tumours in family members of RA patients. In the present study, we used the Swedish data resources on registered families and medically diagnosed RA and cancer, all with a national coverage, to analyse risks of cancer in family members of RA patients, with a specific aim to settle the issue on possible shared genetic risk factors for cancer and RA.

The RA research database was constructed by linking the Multigeneration Register (persons born in Sweden in 1932 and later are linked to their parents) to the Swedish Hospital Discharge Register (all hospital discharges with dates of hospitalization and diagnoses since the 1960s with a complete nation-wide coverage since 1986) and to the nation-wide Swedish Cancer Registry (cancers from 1958 to 2004). The database contains 11.5 million individuals among whom a total of 50 354 RA patients were identified. Details of the data sources and methods can be found in our previous publications [5, 6]. In the analysis of familial risks, parents were considered probands and standardized incidence ratios (SIRs) were calculated for offspring, who were followed until 31 December 2004. SIRs were calculated as the ratio of observed (*O*) to expected (*E*) number of cases. The expected number of cases was calculated for age (5-yr groups), sex, period (5-yr groups), region and socioeconomic status-specific SIRs.

Familial risks between RA and cancer were examined in two ways (Table 1): risk of a specific cancer in offspring whose parents were diagnosed with RA (excluding parent–offspring pairs with the concordant cancers), and risk of RA in offspring whose parents were diagnosed with a specific cancer (excluding parent–offspring pairs with RA). We wanted to make sure that we examined familial risks between discordant diseases, RA and a specific cancer, by excluding families with concordant disease. However, familial diseases were so rare that the exclusions did not change the results. The SIR for no offspring cancer was changed when a parent was diagnosed with RA. SIRs for RA were decreased in offspring whose parents were diagnosed with tumours of the oesophagus (0.53), colon (0.85), breast (0.84) and ovary (0.61). The analysis was repeated for siblings, which