

Anti-TNF therapy and malignancy in spondyloarthritis in the Leuven spondyloarthritis biologics cohort (BIOSPAR)

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Abstract

Objective

To report the incidence of malignancy in a large single-centre cohort in Belgium of patients with spondyloarthritis (SpA) treated with one or more anti-TNF therapies and to compare the results with the incidence of malignancy in the Belgian population.

Methods

From September 2000 until March 2010, all SpA patients that started treatment with one or more anti-TNF therapies were included in this single-centre prospective longitudinal observational study. The primary outcome of this study was the incidence of malignancy after starting anti-TNF treatment. Incidence rates were compared with the incidence rates of malignancy in Belgium in 2008 for the 45–50 year-old population, as documented by the Belgian Cancer Registry.

Results

231 patients with a mean age of 47.86 y were included for a total of 1020.74 patient years of treatment and 1199.83 patient years follow-up after the start of treatment. In our study population, 6 out of 231 patients (2.6 %) developed a malignancy after the start of anti-TNF treatment.

The overall incidence rate of malignancy in our study population is 500.1 per 100000 patient years, indicating a higher incidence compared to the Belgian population. We see a higher incidence rate in females as well in males; standardised incidence ratios are in the same range for both (154.3 for females and 130.6 for males).

Conclusion

We see a tendency towards a higher incidence of malignancy in SpA patients treated with anti-TNF therapy. However, it is not clear whether this increased risk is disease-related or treatment-related.

Key words

spondyloarthritis, ankylosing spondylitis, psoriatic arthritis, malignancy, TNF-alpha, anti-TNF therapy

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Introduction

The spondyloarthritis concept includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, arthritis associated with inflammatory bowel disease (IBD-SpA), juvenile and undifferentiated SpA (1). The overall prevalence of SpA in a Caucasian Western European population is estimated at 1.9% (2). With the exception of some cases of reactive arthritis, these disease entities follow a chronic course with variable disease activity, ultimately leading to disease progression and damage to the spine, joints, tendons and/or ligaments. Quality of life may be severely compromised by pain and loss of anatomical and functional integrity (1). The classical therapeutic options for the management of SpA are limited and often unsatisfactory. Over the past few decades, treatment has consisted mainly of non-steroidal anti-inflammatory drugs and physiotherapy, which are considered the cornerstone of treatment. In contrast with RA, disease-modifying anti-rheumatic drugs (DMARDs) appear to work only to a limited extent in peripheral arthritis but not in axial disease (3). The development and use of biological therapies in the last several years, with agents that specifically inhibit cytokine pathways, such as the tumour necrosis factor / (TNF)-antagonists, has opened new perspectives for the clinical approach to patients with SpA (3, 4). There is extensive and consistent evidence that these agents form an effective therapy in SpA with clear clinical benefits in the short and the long-term (5-7). Long term safety of anti-TNF treatment is now being studied extensively (8). The occurrence of malignancy has been considered as a possible adverse event because TNF-alpha plays an important role in host defense and in the pathobiology of cancer. It is now clear that TNF- α plays a paradoxical role in the evolution and treatment of malignant disease. The anti-cancer actions of TNF- α can be explained by the direct effects on tumour cells, but also by indirect effects on host stroma. Also, under specific circumstances, TNF- α has cytotoxic effects on the vascular endothelium, and is known to modulate

endothelial procoagulant properties. In this way, therapeutic administration of high doses of TNF- α can destroy tumour vasculature, inducing apoptosis and necrosis of tumour cells (9). On the other hand the chronic production of endogenous TNF- α in the tumour microenvironment enhances tumour development and spread (9). It is also believed to induce other cytokines, angiogenic factors and MMPs, as well as to contribute to DNA damage. In this way, TNF- α enhances growth and survival of tumour cells (9, 10).

Large amount of data is available about the background risk of cancer in patients with rheumatoid arthritis (11). There is an increased risk for lymphomas among RA patients but a reduced risk for colorectal cancers. In contrast data about the background risk in patients with SpA and PsA are scarce. The incidence of malignancy in a large prospective cohort of patients with established PsA did not differ from the general population (12).

A large Swedish study concluded that there is no overall increased risk for cancer in AS, but there might be site-specific differences; the risk of rectal cancer was decreased and the risk of kidney cancer was increased. The use of non-steroidal anti-inflammatory drugs and therapeutic radiation, used as a treatment during the 1950s, may account for these differences. Results about the incidence of lymphomas in PsA are not unequivocal (13-15).

Data on cancer risk in patients receiving treatment with anti-TNF agents is mostly available for RA. Recent studies report a significantly higher occurrence of lymphomas and solid tumours, in patients receiving anti-TNF therapy (16-18) but could not be confirmed in others (19-21). There seems an increased incidence of skin cancers in patients with RA treated with biologics but is still unclear if this is entirely due to the treatment (20, 22).

As far as SpA is concerned, only limited data are available. A recent meta-analysis about adverse events including 6 studies with infliximab, 7 studies with etanercept and 2 studies with adalimumab reported one case of basal cell carcinoma in a placebo arm. The treat-

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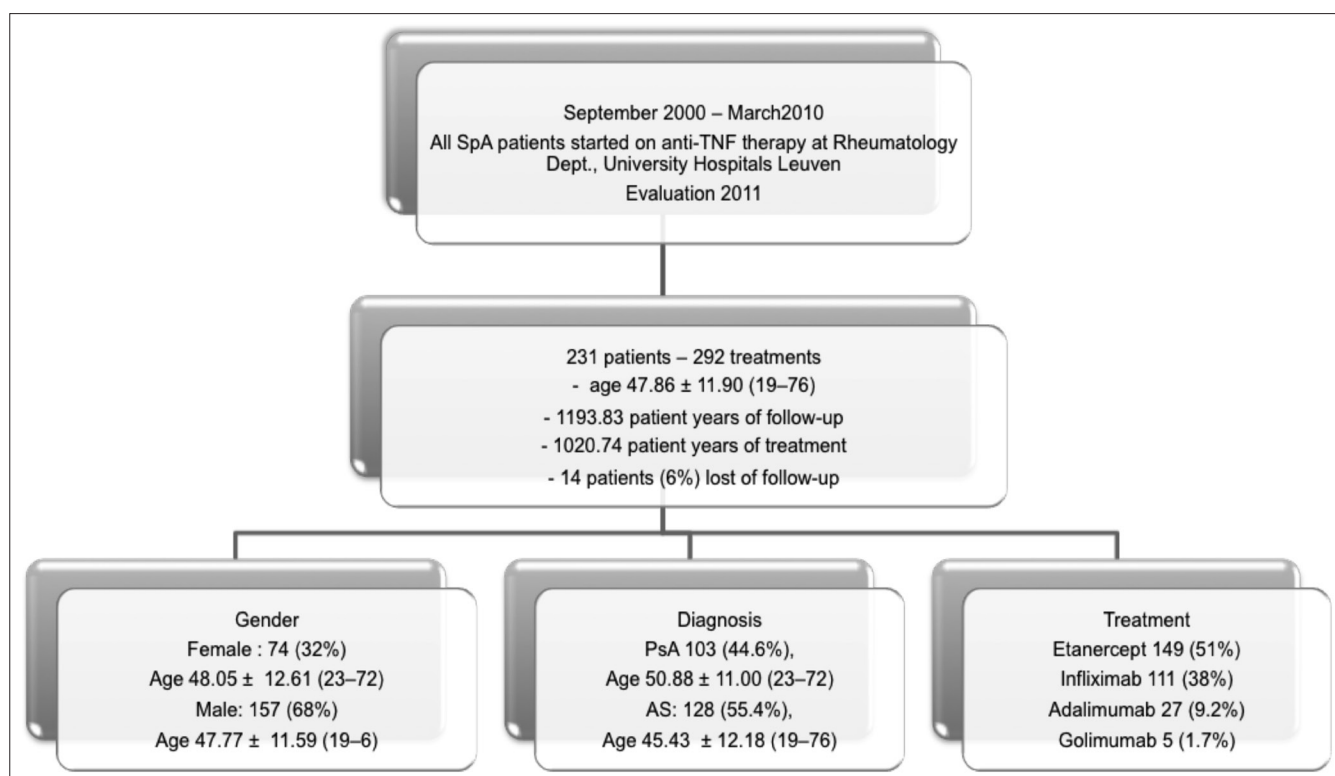


Fig. 1. Overview of characteristics of all patients studied.

ment exposure in all these studies did not exceed 50 weeks (23). A systematic safety follow up in a cohort of 107 SpA patients reported 1 PsA patient who developed a spinocellular carcinoma of the skin at week 82 of infliximab treatment (24).

To contribute to the assessment of cancer risk in SpA patients treated with TNF-blockers, we evaluated all patients treated in our centre at the University Hospitals Leuven with TNF-blockers since these drugs became available and this over a period of 10 years.

Patients and methods

Study population

Since September 2000, the demographics, clinical and biological data, comorbidities and data about treatment of all SpA patients that started anti-TNF treatment at the Leuven University Hospital are recorded prospectively (BIOSPAR database). In case of intolerance or inefficacy, one anti-TNF therapy could be switched to another so that some patients received more than one type of anti-TNF treatment. We evaluated the occurrence of malignancies in the BIOSPAR database until

March 2010 in this prospective longitudinal observational study. Patients were diagnosed according the current classification criteria and treatment decisions were made in conformity with the Belgian reimbursement criteria. The study was approved by the local ethics committee.

Control group

As a control group we used the results of the 2008 analysis of the cancer incidence in the 45–50 years old Belgian population by the Belgian Cancer Registry, which corresponds to the mean age of our study population, and the 2008 analysis of the cancer incidence of the whole Belgian population (25).

Outcome measure

The primary outcome of this study was the incidence of malignancy after starting anti-TNF treatment.

Statistical analysis

Descriptive statistics and statistical analysis was performed using Microsoft Excel software. Continuous variables were summarised by the mean and the standard deviation. In case of

a large range of distribution, the median was also calculated. Malignancy incidence per patient group and per therapy is shown as a fraction and as a percentage. Incidence rates are shown per 100,000 patient years of follow-up. To compare the study population with the control group, standardised incidence ratios (SIR) are calculated. When the SIRs are >100, this suggests an increased risk of cancer.

Results

A total of 231 patients with SpA that were treated with one or more types of anti-TNF therapy were included in this retrospective cohort study. A total of 128 (55.4%) of them were diagnosed with AS and 103 (44.6%) with PsA. Patient age varied between 19 and 76 years old and the average age was 47.86 years. Anti-TNF treatment came down to etanercept, infliximab, adalimumab or, most recently, golimumab treatment. An overview on the study population characteristics is shown in Figure 1. Of all patients, 178 were treated with only one TNF-blocker, 45 patients were treated with two TNF blockers and 8 patients with three dif-

ferent TNF-blockers. A total of 14 patients (6%) were lost to follow-up, of whom 12 were lost to follow-up after the start of their first anti-TNF treatment and 2 were lost to follow-up after their second anti-TNF treatment. All 8 patients that started a third anti-TNF therapy were still in follow-up at the time of analysis. Although not all data were available for every patient, all patients were included in this study in order to provide a correct idea of cancer occurrence in our patient population.

Six out of 231 patients (2.6%) developed a malignancy after the start of anti-TNF treatment. The overall incidence rate of malignancy was 500.1 per 100,000 patient years. Of all patients with malignancy, two were AS patients that were treated with infliximab and three were PsA patients that were treated with etanercept. One patient was diagnosed with cancer 106 weeks after the start of etanercept but had switched to adalimumab 23 weeks before. Incidence rates for PsA were more than two-fold higher than that for AS. The mean age at diagnosis of malignancy was 61 years. All patients were diagnosed after more than 2 years of treatment. The characteristics of patients developing a malignancy are summarised in Table IA. In 2 patients anti-TNF treatment was discontinued because of the diagnosis of malignancy. All other 4 patients continued their treatment. The male/female ratio among patients developing malignancy was 1, but in general there were two times more male SpA patients in our population so that the incidence rate for malignancy in female SpA patients was more than two-fold higher than that in males: 770.1/100,000 patient years versus 370.2/100,000 patient years respectively. All 3 female patients developed breast cancer or a premalignant breast condition. In the male patients group, one developed bladder cancer, another developed a malignant mesothelioma and a third developed a basocellular carcinoma of the skin. Malignancy incidence in the control population aged 45–50 year is 483.3/100,000 person years for women and 283.4/100,000 person years for men. Standardised incidence ratios indicated a higher incidence of malignan-

Table I. characteristics of 6 patients developing a malignancy during anti-TNF treatment (table 1a) and of those 3 patients with a history of malignancy before starting anti TNF treatment (Table 1B).

A							
Patient n°	Gender	Type of SpA	Type of anti-TNF	Age (yrs)	Disease duration (wks)	Treatment duration (wks)	Discontinuation of anti-TNF
1	Male	AS	Infliximab	72.35	943.80	320	Yes
2	Male	AS	Infliximab	67.02	2048.28	285	No
3	Female	PsA	Infliximab	61.90	305.24	262	No
4	Male	PsA	Etanercept	57.69	635.44	232	Yes
5	Female	PsA	Etanercept	56.19	794.04	355	No
6	Female	PsA	Etanercept+ Adalimumab	51.92	204.36	129	No
B							
Patient n°	Gender	Type SpA	Type anti-TNF	Type of malignancy	Age (yrs)	Relapse during treatment anti TNF	
2	Male	AS	Infliximab	Basal cell carcinoma	46.15	Yes	
7	Female	PsA	Etanercept	Breast cancer	37.76	No	
8	Male	AS	Etanercept	Chronic myeloid leukaemia	35.18	No	

PsA: psoriatic arthritis; AS: ankylosing spondylitis; Age: age at diagnosis of malignancy in years.

Disease duration: disease duration at diagnosis of malignancy in weeks.

Treatment duration: treatment duration at diagnosis of malignancy in weeks.

cy in our study population compared to the control population with a comparable mean age, with a slightly higher incidence for female than for male patients (154.3 for females and 130.6 for males). If compared to the incidence in the general Belgian population a different trend was found. The malignancy incidence in the general Belgian population (all age groups) is 386.7/100,000 for women and 536.3/100,000 for men. In our study the standardised incidence ratios (SIRs) shows a higher incidence in women but not in men (199.1 for females and 69.2 for males) compared to the general population (Table II).

We also report 3 patients that started anti-TNF treatment despite a history or previous diagnosis of malignancy. One of them, who had a history of basocellular carcinoma developed a new basocellular carcinoma during treatment with anti-TNF therapy (Table IB). Four out of six patients developing a malignancy had a history of smoking as well as all three patients starting TNF-blockade despite previous diagnosis of a malignancy.

Discussion

We report a possible increased incidence of malignancies in SpA patients

treated with anti-TNF- α treatment. Already from the early beginnings there were some concerns about potential induction of cancer by using TNF blockers. TNF-alpha has a dual role in the development and treatment of malignant diseases. TNF-alpha exerts a direct anti cancer effect on tumour cells and tumour vasculature. Besides chronic TNF- α production enhances tumour development and spread. Using anti-TNF blocking strategies potentially may eliminate the direct anti cancer effect and enhance tumour development (9). Noteworthy is that some chronic inflammatory conditions are associated with an increased incidence of specific tumours such as lymphomas in rheumatoid arthritis and colorectal cancers in Crohn's disease (11). From the earliest days of anti-TNF treatments a large efforts is made to collect data about the incidence of malignancies in patients treated with TNF blockers. Large amount of data is available for Crohn's disease and rheumatoid arthritis but is scarce for SpA and PsA. Several large prospective cohorts with sufficient time to treatment exposure are needed in different backgrounds to evaluate this risk appropriately. We report the incidence in a prospective

Table II. Malignancy incidence in study and control population and standardised incidence ratios.

Incidence rates of malignancy in the study population	
Female	770.1/100,000 person years
Male	370.2/100,000 person years
Incidence rates of malignancy in the control population (for age group 45–50)	
Female	499.1/100,000 person years
Male	283.4/100,000 person years
Standardised incidence ratios (SIRs)	
Female	154.3
Male	130.6
Incidence rates of malignancy in the study population	
Female	770.1/100,000 person years
Male	370.2/100,000 person years
Incidence rates of malignancy in the control population (global)	
Female	386.7/100,000 person years
Male	536.3/100,000 person years
Standardised incidence ratios (SIRs)	
Female	199.1
Male	69.2

SIR: (IR study population / IR control population) * 100; IR: incidence rate.

monocentric cohort of SpA patients and patients with PsA (BIOSPAR). Cancer risk is usually estimated by SIRs. It is obvious that the selected denominator may influence the estimated risk. In this study two different denominators were used, giving some conflicting results. Based on the incidence of malignancy in the Belgian population age between 45–50 years, the standardised incidence ratios obtained in our study indicate that the risk of malignancy is higher in the SpA population treated with anti-TNF therapy in comparison to the Belgian population. The choice of this age group is based on the mean age of our patient population. It is not clear whether this increased risk is disease-related or treatment-related. Since the decision to start anti-TNF treatment was made after careful consideration by the treating physician instead by randomisation, there is a strong probability of confounding by indication. It is not excluded that patients with SpA or PsA and high disease activity are more at risk for development of malignancies as seen in rheumatoid arthritis. Unfortunately such a data is not available in SpA and PsA. On the other hand reducing disease activity should then reduce the risk of malignancies. We were not able to correct for the effect of cumulative disease activity and pos-

sible concomitant treatments. Given the small number of malignancy events per anti-TNF treatment it is impossible to evaluate and to compare the malignancy risk for the different anti-TNF treatments in our study. An alternative explanation is that the setting of a prospective longitudinal cohort increases awareness and improves reporting, so reflecting an increased detection rate rather than a true disease-related risk increase (26).

A higher incidence of malignancy in PsA is here reported, but it must be pointed that all females developing malignancy were PsA patients and gender is a possible confounder in this finding. Incidence rates are higher in the female population, with all three patients developing breast cancer. This is consistent with the finding that in the 45 to 50 years age group of the Belgian population, the incidence of malignancy is higher in females than in males. Here also, this higher incidence is mainly explained by a high incidence of breast cancer in this age group (accounting for about 54% of all malignancies). In the older age categories of the Belgian population for example, the situation is the contrary, with a higher incidence of malignancy in males than in females. Such differences in incidence rates make it important to choose the most

representative control group, in this case the 45 to 50 years age group of the Belgian population. This is illustrated by the fact that if compared to the whole Belgian population we found an increased SIR in female patients but decreased SIR in male patients.

A remarkable finding is that all patients were diagnosed with malignancy more than 2 years after they started anti-TNF treatment, at least suggesting a possible temporal relationship with the treatment. This is in contrast with the findings in the single center series and systematic review from Nannini *et al.*, that showed that a large proportion of malignancies was diagnosed within the first 12 weeks of therapy (23). From a biological perspective it is unlikely that a clinically detectable tumour develops within 12 weeks of treatment exposure. It is suggested that at least part of the detected malignancies were present before starting therapy, highlighting the importance of screening for malignancy before starting anti-TNF therapy. Of all patients that were diagnosed with malignancy after starting anti-TNF treatment, only two discontinued their treatment. Three patients started anti-TNF therapy despite the fact that they had a history or previous diagnosis of malignancy. In all cases, the possible relationship with the treatment was discussed with the patients but all of them considered the benefits of treatment, especially the impact on quality of life, more important than potential risks of relapse of the tumour. In our study population, only one patient so far relapsed from a mild type of cancer. Nevertheless, given the results of this study, safety concerns are rising regarding anti-TNF treatment in these patients. In making such decision, benefits and risks must be carefully weighed out and discussed in consultation with the patient.

Previous studies did not reveal an increased incidence of malignancy in SpA. Most studies have a short duration of follow up in contrast to ours.

There is a need for further investigations with focus the background risk of malignancies and possible additional role of disease severity in this specific patient population.

In summary we report a tendency towards a higher incidence of malignancy in SpA patients that are treated with anti-TNF therapy with incidence rates that are higher in females, consistent with the available demographic evidence in the Belgian population in 2008. Malignancy seems to have been only a relative contra-indication for continuation or start of anti-TNF therapy in our study population. These data from clinical practice contribute to the evidence that might guide clinicians to make weighted decisions in their treatment of severe refractory SpA patients.

Key messages

- In a daily practice cohort of SpA patients treated with TNF blockers we found a tendency towards an increased incidence of malignancies.
- The reason for the increased risk is not clear because of possible confounding by indication.
- Current data might help in guiding clinicians to make weighted decisions while treating their severe SpA patients.

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