Cancer in Patients with Rheumatic Diseases Exposed to TNF Antagonists

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Objective: To describe the risk of cancer in patients exposed to tumor necrosis factor (TNF) antagonists.

Methods: The following 2 clinical cohorts were studied: (1) BIOBADASER 2.0: a registry of patients suffering from rheumatic diseases exposed to TNF antagonists (2531 rheumatoid arthritis (RA), 1488 spondyloarthropathies, and 675 other rheumatic conditions); and (2) EMECAR: a cohort of 789 RA patients not exposed to TNF antagonists. Cancer incidence rates (IR) per 1000 patient-years and incidence rate ratios (IRR) were calculated for BIOBADASER 2.0 and EMECAR patients. The IR over time in BIOBADASER 2.0 patients was analyzed by *joinpoint* regression. The IRR was estimated to compare cancer rates in exposed versus nonexposed RA patients. Standardized incidence and mortality ratios (SIR, SMR) were also estimated. Risk factors for cancer in patients exposed to TNF antagonists were investigated by generalized linear models.

Results: The SMR for cancer in BIODASER 2.0 was 0.67 (95% CI: 0.51-0.86), and the SIR was 0.1 (95% CI 0.03-0.23). The IR in RA patients exposed to TNF antagonists was 5.8 (95% CI: 4.4-7.6), and the adjusted IRR was 0.48 (95% CI: 0.09-2.45). The IR in patients with previous cancer was 26.4 (95% CI: 4.1-171.5). Age, chronic obstructive pulmonary disease, and steroids were associated with a higher risk of developing cancer. The IR decreased after the first 4 months of exposure, without statistical significance.

Conclusion: Overall cancer and mortality rates in patients with rheumatic diseases exposed to TNF antagonists are no higher than in the background Spanish population. However special attention should be paid to elderly patients, those with previous cancers, and patients treated with steroids.

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Tumor necrosis factor (TNF) was first described as a macrophage-derived endogenous mediator able to induce hemorrhagic necrosis in cancer cells in vitro (1,2). It regulates apoptosis, angiogenesis, cell differentiation, and cell migration. TNF is also related to tumor development and tumor progression (3), and the cachexia of sepsis (3,4). Trials with both TNF and TNF antagonists in cancer patients have attempted to modulate the activity of this cytokine, without clear success (5-10).

TNF antagonists have been successfully incorporated in the treatment of immune-mediated rheumatic diseases, based on the central role of TNF in inflammation. A meta-analysis of clinical trials found a 3-fold risk of malignancy in rheumatoid arthritis (RA) patients exposed to TNF antagonists compared with nonexposed patients

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(11). Also, there are reports of lymphomas that improve after discontinuing the TNF antagonist (12). Conversely, several long-term studies from drug registries failed to detect an increased risk of cancer in RA patients exposed to TNF antagonists (13-17). Some of the unresolved questions raised by these studies include the reasons for disparities between data from clinical trials and registries, the risk of cancer in patients with previous cancers, and the risk of cancer for the different TNF antagonists and indications.

Accordingly, the objective of the present study was to analyze the risk of cancer in patients with rheumatic diseases, including RA patients exposed to TNF antagonists, especially those with previous cancers, and to compare the observed rates with nonexposed RA patients and the general population.

METHODS

The following 2 clinical cohorts were studied: an ongoing cohort of patients with rheumatic diseases exposed to TNF antagonists (BIOBADASER 2.0, 2001-September 2008), and a closed cohort of RA patients who were not exposed to TNF antagonists (EMECAR, 1999-2005). The expected cancer rates in the population of Spain were obtained from GLOBOCAN.

BIOBADASER 2.0

This cohort is part of a larger national drug safety registry of patients with rheumatic diseases established in 2001 (BIOBADASER) (18,19) who were treated with biologic response modifiers. BIOBADASER generates a cohort of patients with any rheumatic disease, starting treatment for the first time with any biologic and followed thereafter. The second phase of BIOBADASER, known as BIOBADASER 2.0, was launched in July 2006. To improve data quality, this registry only includes data from 14 large public hospitals.

Patients entering the registry are followed and evaluated at the time an adverse event or a change in biological therapy occurs. Data are collected at 3 levels: patient (gender, date of birth, diagnosis, date of diagnosis, comorbidities, and risk factors), treatment (types of biologics and dates of initiation and of discontinuation, concomitant treatment for the rheumatic disease, disease activity, and chemoprophylaxis of tuberculosis preceding treatment), and adverse event (AE; date of occurrence, type and classification of AE according to the Medical Dictionary for Regulatory Activities (MedDRA), severity, outcome, and concomitant treatments at the time of the AE).

For the purpose of our study, only those patients receiving TNF antagonists in BIOBADASER 2.0 were analyzed. For the estimation of risk in exposed versus unexposed inflammatory patients, only RA patients were analyzed. Once a year, participating hospitals are advised to update information on all patients, after which 10% of their charts are randomly selected and audited. Additionally, patients who previously signed an informed consent document are contacted yearly by project managers to confirm whether they are alive or have been admitted to a hospital in the past year.

The registry protocol and materials of BIOBADASER 2.0, available online at (http://biobadaser.ser.es/biobadaser/eng/index.html), were approved by the Ethics Review Committee of the Hospital Ramon y Cajal (Madrid), which acted as the central Committee.

EMECAR

The EMECAR cohort has also been described previously (20). It comprised 789 patients who were not exposed to TNF antagonists, randomly selected from the databases of 34 Spanish tertiary hospitals and representative of RA patients. All but 2 hospitals were included in BIOBADASER 2.0. Patients were prospectively followed at yearly visits between March 1999 and June 2005, according to a structured protocol. Clinical expression, disease activity, progression, and, especially incident comorbidity, were all recorded during each visit. All data collection forms were audited on receipt, and vital status data were confirmed through local demographic information. The protocol of the EMECAR study was reviewed and approved by the Ethics Review Committee of the Hospital de la Princesa (Madrid), and all patients gave their informed consent to participate.

For the purpose of the study, all data concerning patients in EMECAR who were treated during the observational period with TNF antagonists, or with any other biologic agent, were censored at the time of the first dose.

GLOBOCAN

The GLOBOCAN database (21) was constructed using the data available in the Descriptive Epidemiology Group of the International Agency of Research on Cancer, which is part of the World Health Organization. Data on cancer incidence are obtained from cancer registries that cover entire national populations, or samples of populations from selected regions. The database includes all types of cancer except nonmelanoma skin cancer. The International Agency of Research on Cancer estimates the number of new and prevalent cancer cases and deaths by site, gender, and age group, as well as mortality from cancer. For this study, we used the 2002 estimates of new cancer cases in the general population over age 15 in Spain.

Case Definition

Diagnosis of cancer was extracted from the medical records and confirmed by (1) direct contact with the patient during the study visit (in EMECAR) (22) or (2) the treating physician (BIOBADASER 2.0). Incident cancer was defined as any new cancer diagnosed during follow-up. Cancers diagnosed within the year before cohort entry were considered to be prevalent and thus not incident.

Cancers occurring after discontinuing TNF antagonists in BIOBADASER 2.0 were analyzed case by case with an oncologist who helped to decide whether the cancer could have been present but undiagnosed during the exposure period.

Exposure

In BIOBADASER 2.0, time of exposure was considered to be the period from the beginning of therapy with a TNF antagonist to the date of the last administration plus twice the half-life of the TNF antagonist (3 days for etanercept, 2 months for infliximab, and 14 days for adalimumab). When a patient was started on a new TNF antagonist within the time of exposure of a prior TNF antagonist, overlapping days were counted as "double exposure" and analyzed separately as a risk factor. Time of observation was the period from cohort entry (date of first biologic) to an incident cancer, censor date (last visit in a lost-to-follow-up patient), death, or September 1, 2008, whichever occurred first.

In EMECAR, time of observation covered the period from the baseline visit until an incident cancer, loss to follow-up, death, beginning of any biological therapy, or end of follow-up (last visit).

Statistical Analyses

The study samples were described using the descriptive statistics indicated by the distribution of variables. To compare differences at baseline between the 2 RA cohorts (EMECAR and the subset of BIOBADASER 2.0), Student's t and χ^2 tests were used.

The statistical approach varied according to the research question. The incidence rate (IR) of cancer per 1000 patient-years with a 95% confidence interval (CI) was estimated in the following: (1) all patients exposed to TNF antagonists (BIOBADASER 2.0): (1a) patients with RA; (1b) patients with a diagnosis other than RA (ankylosing spondylitis, psoriatic arthritis, and others); (1c) patients previously diagnosed with cancer. Additionally, the IR was estimated by type of TNF antagonist. (2) RA patients who were not exposed to a TNF antagonist (EMECAR). The IR was estimated for all cancers together, and by type of cancer.

The IR of cancer in patients with RA in BIOBADASER 2.0 was compared with the IR in EMECAR by using the incidence rate ratio (IRR). The results are presented both unadjusted and adjusted for age, gender, duration of disease, disease severity at baseline, smoking, methotrexate and glucocorticoid use, and chronic obstructive pulmonary disease (COPD) at entry.

Thereafter, we estimated the standardized incidence ratio (SIR) as the ratio of observed cases to expected cases in the general population of Spain (Source: GLOBOCAN, World Health Organization program 2002) stratified by age and gender. The SIR was obtained for all cancers together, by type of cancer, and by type of rheumatic disease.

The standardized mortality ratio (SMR) with 95% CI was calculated by the indirect method, stratified by age and gender, using 2002 data for cancer mortality in the Spanish population (data were obtained from the National Institute of Statistics, *Instituto Nacional de Estadística*, at http://www.ine.es).

Risk factors for cancer in all patients exposed to TNF antagonists were investigated by generalized linear regression models assuming a Poisson distribution of the data. Bivariate and multivariate analyses were performed by backward stepwise selection of all variables with a $P < 0.2$ in the bivariate analysis. The following variables were included in the models: gender, age, disease duration, diagnosis, baseline concomitant treatment, comorbidity, previous cancer, biologic molecule (adalimumab, etanercept, infliximab), sequence of treatment (as some patients may have been treated with more than 1 TNF antagonist), and double exposure. Results were expressed as IRRs with their 95% CIs.

To analyze whether length of exposure may be playing a role in the risk of cancer, we estimated the IR of cancer in 4-month periods and cumulative periods up to 3 years from the start of the TNF antagonist in BIOBADASER 2.0. In addition, we conducted trend analysis by joinpoint regression analysis using the software provided by the Surveillance Research Program of the US National Cancer Institute (23). This analysis allows us to identify points (joinpoint) where a significant change in the linear slope of the trend occurs (24). The analysis starts with zero joinpoints, which is a straight line, and tests whether 1 or more joinpoints are significant. A LOWESS (locally weighted scatterplot smoothing) curve was also fitted to show a change in the trend.

All analyses were done with Stata 10.0 (Stata Corp., College Station, TX, 2008).

Role of the Funding Source

The researchers had complete freedom to design and perform the analyses presented, independent from the funding sources, which never had access to individual data. The funding in the cohorts analyzed was used to motivate data collection in the participating centers and to pay the monitors of the respective studies.

RESULTS

Figure 1 depicts the number of patients and total patient-years of exposure or observation in the different databases and subsamples. The median exposure time in BIODASER 2.0 was 3.1 years (25th-75th percentiles: 1.4-4.9 years), with a maximum of 8.9 years. Patients in EMECAR were slightly older and had lower disease activity, as measured by the DAS28, at the beginning of follow-up than RA patients in BIOBADASER 2.0 (Table 1).

Eighty-one new cancers were reported in BIOBADASER 2.0, corresponding to an IR of 5.17 (95% CI: 4.16- 6.43) per 1000 patient-years of exposure. The IR of all types of

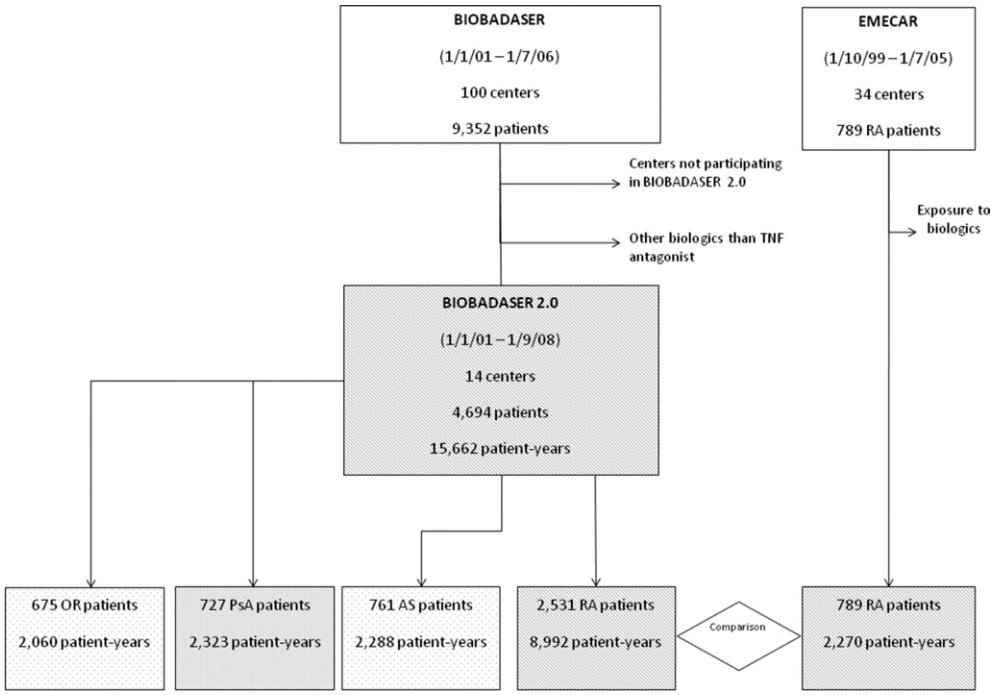

Figure 1 Study diagram showing the databases utilized and the analyses performed. Shaded boxes include the analyzed subsets. RA, rheumatoid arthritis; AS, ankylosing spondylitis, PsA, psoriatic arthritis; OR, other rheumatic diseases.

cancers for infliximab, etanercept, and adalimumab was 5.98 (95% CI: 4.46-8.01), 4.46 (95% CI: 2.99-6.65), and 4.43 (95% CI: 2.51-7.79) per 1000 patient-years, respectively. The most frequent type of cancer was non-melanoma skin cancer (IR: 1.21; 95% CI: 0.77-1.90), followed by breast cancer (IR: 0.70; 95% CI: 0.39-1.27), lung cancer (IR: 0.57; 95% CI: 0.30-1.10), and colon and rectal cancer (IR: 0.51; 95% CI: 0.26-1.02).

Fifty-two new cancer cases were reported in RA patients in BIOBADASER 2.0 and 28 in EMECAR. The IR of cancer in BIOBADASER 2.0 and EMECAR patients was 5.78 (95% CI: 4.41-7.59) and 12.33 (95% CI: 8.51-

Table 1 Characteristics of the Study Cohorts

Database	BIOBADASER 2.0 (rheumatic disease patients treated with TNF antagonists)	BIOBADASER 2.0 (only RA patients treated with TNF antagonists)	EMECAR (RA patients not treated with TNF antagonists)
N by diagnoses	2531 RA 761 AS 727 PsoA 675 others[a]	2531 RA	789 RA
Patient-years of follow-up	15,662[b]	8992[b]	2270
Mean patient-years of follow-up ± SD	3.32 ± 2.2	3.54 ± 2.29	2.88 ± 1.57
Age, mean ± SD	52.64 ± 15.22	58.25 ± 13.70	61.43 ± 13.07[c]
Women, *n* (%)	2927 (62)	2026 (80)	568 (72)[c]
Disease duration (yr), mean ± SD	10.56 ± 8.60	10.28 ± 8.20	10.12 ± 7.94
Rheumatoid factor positive, *n* (%)	NA	2317 (91)	578 (75)[c]
DAS28 at baseline, mean ± SD	NA	5.52 ± 1.25	4.25 ± 1.40[c]
COPD, *n* (%)	82 (2)	56 (2)	63 (8)[c]
Smokers, *n* (%)	493 (10)	220 (9)	274 (35)[c]

RA, rheumatoid arthritis; AS, ankylosing spondylitis; PsoA, psoriatic arthritis; SD, standard deviation; NA, not applicable; DAS28, disease activity score based on 28 joint counts; COPD, chronic obstructive pulmonary disease.
[a]Other rheumatic diseases: juvenile idiopathic arthritis, undifferentiated spondyloarthritis, enteropathic arthritis, seronegative chronic polyarthritis, Beçhet's disease, seronegative chronic oligoarthritis, systemic lupus erythematosus, SAPHO syndrome, reactive arthritis, Still's disease, uveitis, undifferentiated juvenile spondyloarthritis, vasculitis, polymyositis/dermatomyositis, juvenile ankylosing spondylitis, Sjögren's syndrome, relapsing polychondritis, sarcoidosis, systemic sclerosis, pyoderma gangrenosum, Muckle-Well's disease, Felty's syndrome.
[b]Exposure.
[c]$P < 0.001$ between RA databases.

Table 2 Cancer Incidence Rate and Standardized Incidence Ratio in Rheumatoid Arthritis (RA) Patients Exposed and Nonexposed to TNF Antagonists, by Cancer Type and Overall

	Exposed RA Patients (BIOBADASER 2.0)		Nonexposed RA Patients (EMECAR)		General Population (GLOBOCAN)
	Adjusted Rate/1000 Patient-years	SIR	Adjusted Rate/1000 Patient-years	SIR	Rate/1000 Person-years
Colon and rectum	0.14 (0.01-0.53)	0.23 (0.03-0.82)	0.20 (0.00-1.13)	0.36 (0.01-1.98)	0.63
Pancreas	0.36 (0.11-0.84)	3.20 (1.04-7.48)	—	—	0.11
Lung	0.69 (0.25-1.51)	1.19 (0.44-2.60)	1.84 (0.73-3.81)	3.47 (1.40-7.16)	0.58
Melanoma of skin	0.15 (0.01-0.55)	1.63 (0.20-5.87)	0.24 (0.00-1.37)	3.84 (0.10-21.41)	0.09
Breast[a]	0.51 (0.25-0.91)	1.11 (0.55-1.98)	0.38 (0.04-1.39)	0.88 (0.11-3.17)	0.89
Cervix uteri[a]	0.05 (0.00-0.31)	0.88 (0.02-4.92)	0.23 (0.00-1.34)	4.09 (0.10-22.76)	0.12
Corpus uteri[a]	—	—	0.17 (0.00-0.97)	1.45 (0.04-8.09)	0.22
Ovary[a]	0.05 (0.00-0.27)	0.50 (0.01-2.79)	0.18 (0.00-1.33)	2.39 (0.06-13.29)	0.18
Prostate[b]	0.27 (0.03-0.98)	0.70 (0.08-2.51)	0.48 (0.05-1.75)	1.85 (0.22-6.67)	0.79
Kidney	0.18 (0.02-0.65)	1.51 (0.18-5.44)	0.23 (0.00-1.31)	2.53 (0.06-14.08)	0.12
Bladder	0.11 (0.00-0.63)	0.31 (0.01-1.75)	—	—	0.35
Brain, nervous system	0.07 (0.00-0.42)	0.84 (0.02-4.68)	0.26 (0.00-1.48)	3.06 (0.08-17.07)	0.09
Thyroid	0.07 (0.00-0.39)	1.55 (0.04-8.62)	—	—	0.04
Hodgkin lymphoma	0.13 (0.00-0.78)	5.28 (0.13-29.43)	—	—	0.03
Non-Hodgkin lymphoma	0.23 (0.04-0.69)	1.49 (0.31-4.35)	0.68 (0.13-2.02)	5.40 (1.11-15.78)	0.16
Leukemia	—	—	0.89 (0.23-2.29)	8.83 (2.41-22.61)	0.12
All sites but skin	3.04 (2.16-4.16)	0.66 (0.47-0.90)	5.60 (3.62-8.27)	1.21 (0.78-1.78)	4.64

SIR, standardized incidence ratio stratified by age and gender.
[a]Females only.
[b]Males only.

17.86) per 1000 patient-years, respectively. The IRR of cancer in exposed versus nonexposed RA patients was 0.47 (95% CI: 0.30-0.74; $P < 0.001$). After adjustment for age, gender, disease duration, severity of RA, methotrexate and glucocorticoid use, and COPD, the IRR was 0.48 (95% CI: 0.09-2.45). Table 2 shows the IR and SIR of cancer in BIOBADASER 2.0 and EMECAR, adjusted to the age and sex distribution of the general population of Spain.

The rate of cancer in BIOBADASER 2.0 was significantly lower than in the background population of Spain [SIR = 0.67 (95% CI: 0.51-0.86)]. Similar results were obtained in the subset of RA patients exposed to TNF antagonists (Table 2), but the rates of cancer in patients with rheumatic diseases other than RA exposed to TNF antagonists did not differ significantly from the general population, as reflected by the SIR in Table 3.

In relation to mortality, the SMR in BIOBADASER 2.0 was 0.1 (95% CI 0.03-0.23) [women: 0.04 (95% CI 0-0.21); men: 0.17 (95% CI 0.05-0.44)]. In RA patients exposed to TNF antagonists, the SMR was 0.09 (95% CI

Table 3 Standardized Incidence Ratio of Cancer in Patients Exposed to TNF Antagonists Suffering from Rheumatic Diseases Other than Rheumatoid Arthritis, by Cancer Type and Overall

	Ankylosing Spondylitis	Psoriatic Arthritis	Other Rheumatic Diseases[a]
Exposure (patient-years)	2288	2323	2060
Colon and rectum	2.38 (0.49-6.96)	1.28 (0.15-4.62)	1.57 (0.04-8.74)
Lung	1.66 (0.34-4.85)	—	—
Prostate[b]	1.10 (0.03-6.13)	1.18 (0.03-6.59)	3.81 (0.10-21.24)
Kidney	—	3.13 (0.08-17.43)	—
Bladder	0.96 (0.02-5.37)	2.06 (0.25-7.42)	—
Non-Hodgkin lymphoma	2.72 (0.07-15.13)	4.84 (0.59-17.48)	—
Leukemia	3.97 (0.10-22.13)	—	—
All sites but skin	0.92 (0.44-1.70)	0.73 (0.33-1.39)	0.35 (0.04-1.27)

The standardized incidence ratio is stratified by age and gender.
[a]Other rheumatic diseases: juvenile idiopathic arthritis, undifferentiated spondyloarthritis, enteropathic arthritis, seronegative chronic polyarthritis, Beçhet's disease, seronegative chronic oligoarthritis, systemic lupus erythematosus, SAPHO syndrome, reactive arthritis, Still's disease, uveitis, undifferentiated juvenile spondyloarthritis, vasculitis, polymyositis/dermatomyositis, juvenile ankylosing spondylitis, Sjögren's syndrome, relapsing polychondritis, sarcoidosis, systemic sclerosis, pyoderma gangrenosum, Muckle-Well's disease, Felty's syndrome.
[b]Males only.

Table 4 Risk Factors for Cancer in 4694 Patients Exposed to TNF Antagonists

	N (%)	Bivariate IRR (95% CI)	Multivariate IRR (95% CI)
Women	2927 (62)	0.71 (0.45-1.15)	0.61 (0.37-0.99)*
Age	53 ± 15[a]	1.04 (1.03-1.06)***	1.04 (1.02-1.06)***
Disease duration (yr)	11 ± 9[a]	0.98 (0.95-1.01)	
Diagnosis			
Rheumatoid arthritis	2531 (54)	1	
Ankylosing spondylitis	761 (16)	0.91 (0.46-1.77)	
Psoriatic arthritis	727 (15)	0.97 (0.49-1.92)	
Others	675 (14)	0.34 (0.12-0.93)*	
Smoking	493 (10)	0.89 (0.41-1.94)	
Previous cancer	24 (1)	5.22 (0.79-34.34)	
COPD	82 (2)	8.22 (3.52-19.20)***	4.91 (1.98-12.19)***
Methotrexate	2103 (45)	1.66 (1.04-2.65)*	
Leflunomide	491 (10)	1.17 (0.52-2.61)	
Other DMARDs	460 (10)	0.71 (0.29-1.76)	
Corticosteroids	1759 (37)	2.15 (1.35-3.42)**	2.05 (1.28-3.28)**
Treatment sequence			
First	4694 (69)	1	
Second and thereafter	2090 (31)	0.81 (0.44-1.47)	
TNF antagonist			
Infliximab	2646 (39)	1	
Etanercept	2137 (32)	0.75 (0.43-1.30)	
Adalimumab	1454 (21)	0.74 (0.39-1.41)	
Double exposure	547 (8)	—	

IRR, incidence rate ratio; CI, confidence interval; DAS28, disease activity score; COPD, chronic obstructive pulmonary disease; DMARD, disease modifying anti-rheumatic drugs.
[a]Mean ± standard deviation.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

0.02-0.25) [women: 0.04 (95% CI 0-0.24); men: 0.16 (95% CI 0.02-0.59)]. In EMECAR, the SMR was 0.98 (95% CI 0.52-1.67) [women: 0.31 (95% CI 0.04-1.11); men: 1.62 (95% CI 0.81-2.89)].

Before exposure to TNF antagonists, 24 patients had had 24 cancers. Most of these were breast cancer (11 cases) and nonmelanoma skin cancer (4 cases). A male patient with psoriasis and a previous basal skin carcinoma developed an incident malignancy following TNF exposure; thus, the IR of cancer in patients with a previous cancer was estimated as 26.4 per 1000 patient-years (95% CI: 4.1-171.5).

Age, RA, COPD, and concomitant use of methotrexate or corticosteroids were associated with a higher risk of developing cancer in patients exposed to TNF antagonists in the bivariate analyses. Previous cancer increased the risk of a new cancer, although this did not reach statistical significance. In multivariate analysis, the best fitted model included older age, COPD, and concomitant use of corticosteroids (Table 4).

In BIOBADASER 2.0 the risk of cancer did not increase with exposure. When analyzed by 4-month periods, the IR of cancer decreased immediately after the fourth month of exposure and rose at the beginning of the second year (Table 5). In the cumulative periods, the IR was found to decrease after the first 4 months and remained largely stable thereafter (Table 5). In both cases,

Table 5 Incidence Rate of Cancer per 1000 Patient-years of Exposure to TNF Antagonists in all Rheumatic Patients of BIOBADASER 2.0, by 4-month Intervals since First Exposure and with Cumulative Exposure

4-mo Intervals of Exposure	Person-years	All Sites N	All Sites IR (95% CI)	Cumulative Exposure (mo)	Person-years	All Sites N	All Sites IR (95% CI)
0-4	1538	10	6.50 (3.50-12.08)	0-4	1538	10	6.50 (3.50-12.08)
4-8	1439	6	4.17 (1.87-9.28)	0-8	2977	16	5.37 (3.29-8.77)
8-12	1340	4	2.99 (1.12-7.95)	0-12	4317	20	4.63 (2.99-7.18)
12-16	1254	8	6.38 (3.19-12.76)	0-16	5571	28	5.03 (3.47-7.28)
16-20	1155	7	6.06 (2.89-12.71)	0-20	6726	35	5.20 (3.74-7.25)
20-24	1065	8	7.51 (3.76-15.02)	0-24	7791	43	5.52 (4.09-7.44)
24-28	988	4	4.05 (1.52-10.79)	0-28	8780	47	5.35 (4.02-7.12)
28-32	902	3	3.33 (1.07-10.31)	0-32	9682	50	5.16 (3.91-6.81)
32-36	832	3	3.61 (1.16-11.18)	0-36	10513	53	5.04 (3.85-6.60)

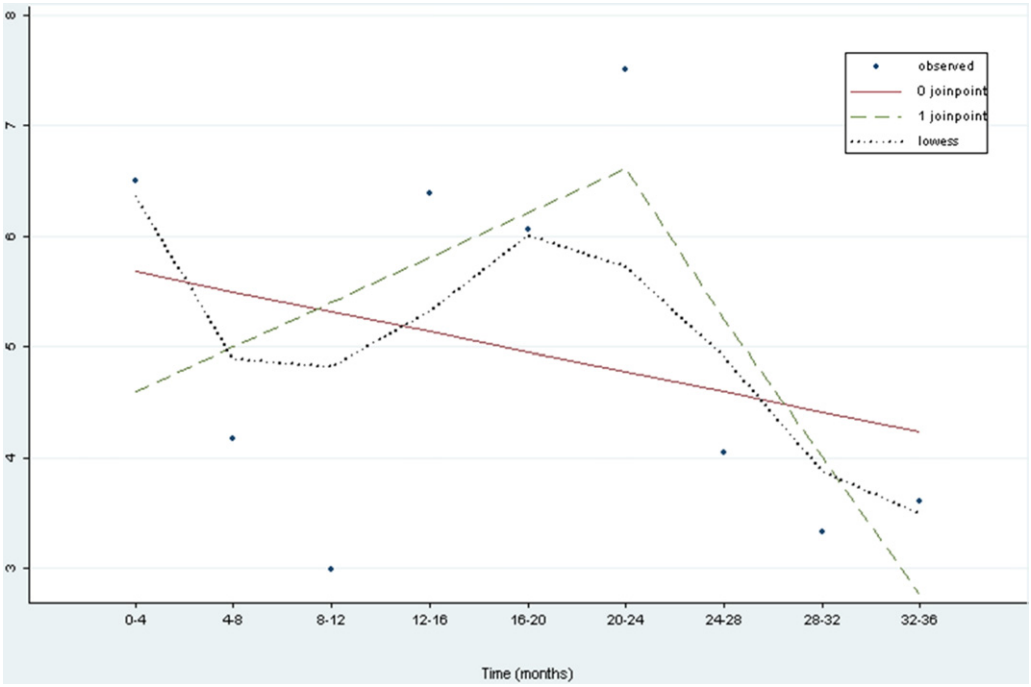

Figure 2 Incidence rate of cancer at different points of exposure to TNF antagonists. Dots represent actual incidence rate. The straight solid line represents the theoretical model of trend fitted with no joinpoint. The dashed line represents the model with 1 joinpoint. The dotted line is the LOWESS curve fitted to the actual points. (Color version of figure is available online.)

the confidence intervals overlapped. Additionally, the model with 1 joinpoint showed a peak around the first 2 years of exposure, whereas in the model with no joinpoint there was a downward trend in the rate throughout (Figure 2). Nevertheless, none of the models achieved statistical significance.

DISCUSSION

In the present study, we found that overall cancer rates in patients exposed to TNF antagonists are no higher than what would be expected in the general population of similar age and gender distribution. Furthermore, the risk of cancer with TNF antagonists may be greater during the first 4 months of exposure than in the long term.

The SIR of overall cancer in RA patients exposed to TNF antagonists in the long term is consistent with previous studies of biologic registries by Askling and coworkers [SIR = 0.9 (95% CI: 0.7 -1.2)] (14), Strangfeld and coworkers [SIR = 0.75 (0.54-1.01)] (25), Geborek and coworkers [SIR = 1.1 (0.6-1.8)] (13), or Wolfe and Michaud [SIR = 1.0 (1.0-1.1)] (26). In contrast, a meta-analysis by Bongartz and coworkers showed a 3-fold increase in the rate of malignancies compared with placebo (11). The latter study did not adjust for exposure time despite a larger number of dropouts in the placebo group during the randomized controlled phase. This could have led to an overestimation of the effect as follow-up time in the treatment group was longer. After correction for follow-up time, the increased risk could not be demonstrated (27,28).

Many cancers in the aforementioned clinical trials of TNF antagonists were reported very early after the initiation of the active drug. Explanations for this may be that (1) they were present before initiating therapy, or (2) they were unmasked by blocking TNF. Another possibility is that signs of cancer may be confounded by active disease, as we have shown previously (22). The experience with biologics registries has shown that the risk of cancer does not increase with longer exposures (17), yet an increase in the first months has not been reliably ruled out. Our study is also unable to demonstrate this initial effect. None of the joinpoint models achieved statistical significance, and it was not possible to construct a model with more than 1 joinpoint due to sample size constraints. However, analysis of the first months of exposure shows a plausible trend toward an increased rate. Merging data from various registries may answer this question. However, there are barriers to merging data from registries, given that background populations and study methodologies may differ (29). A US study reports a shorter time to development of lymphomas in RA patients treated with TNF antagonists than with methotrexate (15).

The risks of lung cancer, leukemia, and lymphoma are higher in RA patients than in the general population (22,30,31). This is counterbalanced by the decreased risks of colorectal cancer and breast cancer. Overall, the risk of cancer in RA is increased only marginally or not at all (32). Accordingly, in RA patients in EMECAR we failed to find an increase in the overall cancer rate compared with the general population in Spain (22). Furthermore,

in our study of RA patients exposed to TNF antagonists, there were 34% fewer cancer cases than expected. Tumorigenesis may be reduced by blocking TNF, as reported in the treatment of cancer (33). Moreover, the risk of dying from cancer is clearly decreased in rheumatic disease patients exposed to TNF antagonists (34), as we have reported previously (35). This may be explained by close patient follow-up, lower rate of comorbidities, and tight control of inflammation. Of note is that our multivariate analysis disclosed an association between developing cancer and the use of corticosteroids, perhaps a surrogate for more severe disease activity, which in turn is associated with a higher risk of hematologic malignancies in RA (36).

An important limitation of our study is the absence of a comparator for nonmelanoma skin cancer. Unfortunately, GLOBOCAN does not include data on nonmelanoma skin cancer, thus precluding the estimation of the observed/expected ratio for this type of cancer, which appears mildly elevated in the present study and may lead to a lower SIR in the general population. Other studies have found an association between RA and nonmelanoma skin cancer (14,34,37,38). Whether TNF antagonists further increase this risk is unclear. The balance between progression and protection by cytokines may be different for different types of cancers, and the effect of blocking cytokines may vary from cancer to cancer.

The increased risk of relapse or second primary cancers in patients treated with TNF antagonists is disputed. In clinical trials, patients with a malignancy before the trial are commonly excluded. In reports in abstract format from the BSR Biologics Registry, no conclusive information was found (39). One of the patients in BIOBADASER had a recurrence of a basal cell carcinoma of the face. Although the number of patients with a prior malignancy was small, reflecting a decision bias to start TNF antagonist therapy, the rate, as well as the elevated risk ratio, clearly argues against starting TNF antagonists in patients with a history of cancer.

The risk of cancer in patients with diseases other than RA is uncertain. The risk of solid tumors, lymphomas, and leukemia is increased in patients with ankylosing spondylitis after medical radiation (40-42), but not in patients who are not exposed to medical radiation (43,44). Patients with psoriasis have a risk of systemic and cutaneous cancer comparable with the risk in the general population, and a modestly increased rate of lymphoma (45-47). On the other hand, some studies show a decreased risk of rectal cancer related to the use of NSAIDs, and an increased risk of unspecified kidney cancer, probably related to frequent radiographic pelvic examinations (48). In our study, patients with spondyloarthritis treated with TNF antagonists do not seem to have an increased risk of malignancies compared with the general population, although the confidence intervals are very wide.

In summary, this study fails to show an increased cancer risk in patients with rheumatic diseases with long-term exposure to TNF antagonists compared with either the general population or patients not exposed to these biologics. This information can contribute to the knowledge of their safety profile. Nevertheless, caution is advised in elderly patients and those with previous cancers, those with COPD, or those treated with steroids, especially during the first months of exposure.

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APPENDIX

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