

Risk of malignancy including non-melanoma skin cancers with anti-tumour necrosis factor therapy in patients with rheumatoid arthritis: meta-analysis of registries and systematic review of long-term extension studies

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Abstract

Objective

To assess the risk of malignancy in patients with rheumatoid arthritis (RA) receiving tumour necrosis factor (TNF) antagonists through a meta-analysis of data from registry studies and systematic review of long-term extension (LTE) studies.

Methods

We systematically reviewed the literature up to January 2010 in the Embase and Medline databases, as well as abstracts from the 2008 and 2009 annual meetings of the EULAR and the ACR. The Mantel-Haenszel method was used to provide a common odds ratio (OR). Statistical heterogeneity was assessed by the chi-square Q test (χ^2). Standardised incidence ratio (SIR) was extracted for post-marketing studies and registries.

Results

The literature search identified 634 articles and 110 abstracts, of which 12 and 5, respectively, were selected for analysis. We could perform a meta-analysis of data from 4 and 3 registries for risk of total malignancy and non-melanoma skin cancers (NMSC), respectively. The pooled OR for total malignancy and for NMSC was 0.81 [95% confidence interval (CI) 0.71–0.94] and 0.79 [0.62–1.02] in TNF antagonist group versus DMARD group, respectively. There was no significant heterogeneity. Among 4 LTE studies and 4 registries, no significant increase in the incidence of total malignancy was noted versus the general population. The only signal may be an increased risk of non-melanoma skin cancers.

Conclusion

Our meta-analysis of data from registries and systematic review of LTE studies did not reveal an increased risk of total malignancy in RA patients receiving anti-TNF therapy.

Key words

TNF- α antagonists, rheumatoid arthritis, malignancy, meta-analysis, systematic review

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Introduction

Rheumatoid arthritis (RA) is the most frequent rheumatic disease in adults. Recently, the advent of biological therapies has represented a revolution for the treatment of active RA. With these new treatments has become the concept of targeted therapy (1, 2). The first biologics which have shown effectiveness in RA were tumour necrosis factor (TNF) antagonists. They are now widely used for treating RA, in particular after methotrexate failure, and even in methotrexate-naïve patients in early and severe RA, in association with synthetic disease-modifying anti-rheumatic drugs (DMARDs) (3-11).

In addition to adalimumab, etanercept and infliximab, which are currently used, 2 new anti-TNF monoclonal antibodies (certolizumab and golimumab) have recently been approved for RA (12-18). Some studies have suggested that RA is associated with an increased risk of malignancy regardless of treatment. In a recent meta-analysis (19), the overall risk of malignancy in RA (including lymphoma) was nearly similar to that of the general population, with a standardised incidence ratio (SIR) of 1.05 [95% confidence interval (CI) 1.01-1.09]. However, patients with RA have an increased risk of lung cancer (SIR=1.63 [1.43-1.87]) and lymphoma (SIR=2.08 [1.80-2.39]) as compared with the general population but a decreased risk of colorectal cancer (SIR=0.77 [0.65-0.90]) and breast cancer (SIR=0.84 [0.79-0.90]) (19). Increased risk of lymphoma in RA was found associated with disease activity and severity (20). This relationship has not been demonstrated for solid malignancies (21).

TNF has a complex effect on carcinogenesis, and studies suggest that inhibition of TNF could enhance or inhibit cancer development. In physiological doses, TNF promotes cell proliferation and thus the growth of tumour (22). However, in large doses, thus activating apoptosis and blocking angiogenesis, TNF could suppress the development of certain cancers. Its impact is likely to vary depending on the types of cancer and stage of carcinogenesis (23).

A meta-analysis of RCTs suggested that 2 anti-TNF monoclonal antibodies

(infliximab and adalimumab) might be associated with increased risk of malignancy (24). This report has been controversial (25, 26). Data from RCTs with etanercept did not find a significantly increased risk in RA patients (27, 28). However, RCTs are limited by their short follow-up, whereas carcinogenesis may last many years. Long-term extension studies compensate for these biases. In registries, patients are followed up for a long time and not selected by strict inclusion criteria that better reflects the daily practice. Some registries found a higher risk of lymphomas in RA patients receiving anti-TNF antagonists than in the general population (29, 30), but results are conflicting regarding risk of solid malignancies and non-melanoma skin cancers.

Our objective was to assess the risk of total (all solid and haematological) malignancy, with a focus on solid and non-melanoma skin cancers (NMSC) in RA patients receiving TNF antagonists by performing a meta-analysis based on data from registries and a systematic review of long-term extension (LTE) studies.

Methods

Study selection

We performed a systematic review of the literature up to January 2010. Bibliographic references were selected from Embase and Medline databases, without limitation to year of publication or journal, and abstracts from 2008 and 2009 annual meetings of the European League Against Rheumatism and the American College of Rheumatology.

We searched Medline via PubMed using the following keywords: arthritis, rheumatoid [MeSH] OR rheumatoid arthritis [all fields] AND (neoplasm [MeSH] OR safety [MeSH]) OR (neoplasm or safety) [all fields] AND (biological therapy [MeSH] OR tumour necrosis factor-alpha [MeSH] OR antibodies, monoclonal [MeSH]) OR (monoclonal antibody OR biological response modifier OR tumour necrosis factor-alpha OR tumour necrosis factor alpha antibody OR tumour necrosis factor-alpha OR anti tumour necrosis factor) [all fields] OR infliximab [substance name] OR (infliximab

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Competing interests: G. Mouterde has received honoraria from BMS, Roche-Chugai (less than 5,000 USD/year); J. Morel has received honoraria from Abbott, BMS, UCB, Pfizer, Roche-Chugai, Nordic Pharma, and MSD (less than 20,000 Euro/year); B. Combe has received honoraria from BMS, Merck, Pfizer, Roche-Chugai, and UCB (less than 10,000 USD/year); the other co-authors have declared no competing interests.

OR remicade) [all fields] OR TNF R-Fc fusion protein [substance name] OR (etanercept OR enbrel) [all fields] OR adalimumab [substance name] OR (adalimumab OR humira) [all fields] OR certolizumab pegol [all fields] OR golimumab [all fields] OR (Drug Combination Disease(W)Modifying(W)Anti(W)Inflammatory(W)Drug OR Dmard) [all fields]. Only English language studies were included. Embase databases were searched with the key words rheumatoid arthritis AND neoplasm AND TNF alpha. In addition, reference lists of the papers initially detected were manually searched to identify additional relevant reports. Articles were initially selected on the basis of their title and abstract, then on the full text. We excluded meta-analysis and all infliximab, adalimumab, etanercept, certolizumab and golimumab RCTs, because results concerning the risk of malignancy have already been reported. To be included, registry studies had to have a comparison group for risk of malignancy (synthetic DMARD group with observed cases or general population, regarding expected cases).

The PICO search strategy was used to translate the research question into epidemiological terms for study retrieval.

- Population included in different studies and registries: adult patients with rheumatoid arthritis (RA) (ACR 1987 criteria or diagnosis made by the rheumatologist).
- Intervention: treatment with TNF alpha antagonists (infliximab, etanercept or adalimumab)
- Comparison:
 - RA patients treated with DMARDs in registries
 - General population in long-term extension studies and registry studies without control group
- Outcome: diagnosis of total malignancies, considered as all solid and haematological cancers or NMSC. Solid cancer excluded myeloma, leukaemia and all types of lymphoma. NMSC included basal and squamous cell skin cancers.

Data collection

One investigator (PLB) selected the articles and collected the data using a

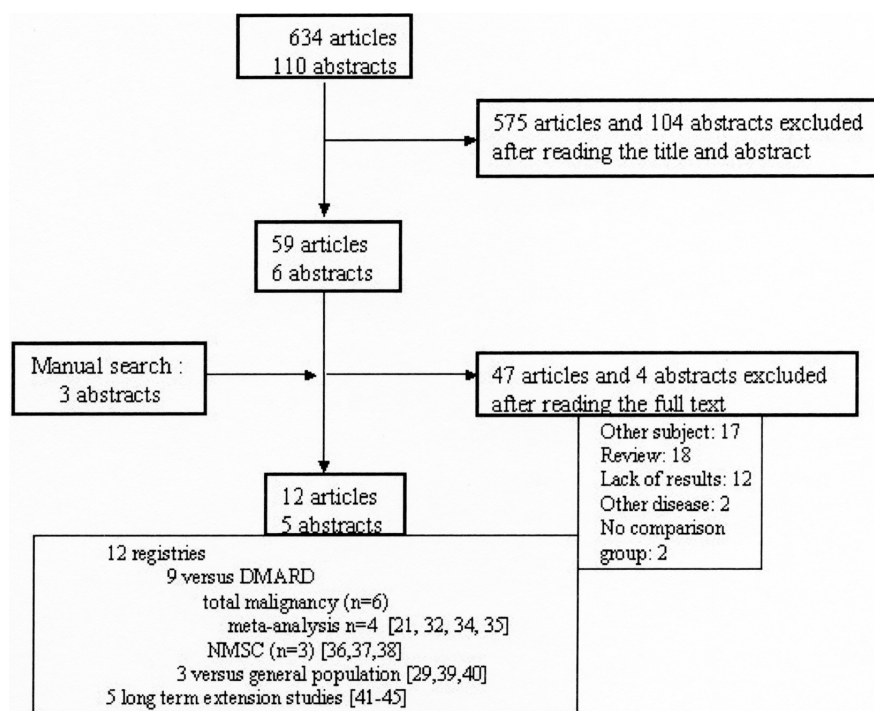


Fig. 1. Flow chart of the selection of articles.

predetermined form. Data were collected on journal, year of publication and author, study design, data source, type of anti-TNF and treatment in the control group, number of patients and patient years in each group, patient characteristics, follow-up time and treatment exposure, total and solid malignancy cases in anti-TNF groups and control groups and odds ratios (ORs), hazard ratios (HRs), relative risk (RR), incidence rate ratio (IRR) or standardised incidence ratio (SIR).

Statistical analysis

The Mantel-Haenszel method was used to provide a common OR estimate and 95% CI for patients receiving anti-TNF *versus* DMARD therapy for registries. Analyses involved use of Revman 5.0 software package developed by the Nordic Cochrane Center. ORs and 95% CIs are shown on forest plots. Statistical heterogeneity was assessed by the chi-square Q test (χ^2), with a significance level of 0.05. Only a fixed-effect model was performed if the heterogeneity was not found significant. SIRs for patients *versus* the general population were extracted for long-term extension studies and registries without DMARD control group.

Results

The literature search identified 634 articles and 110 abstracts, among which 59 and 6, respectively, were pre-selected on the basis of the title and abstract. Of these, 12 and 5 reports, respectively, were selected for analysis on the basis of the full text (21, 29, 31-45). Figure 1 summarises the selection of articles. Of 17 studies, 12 were registries and 5 LTE studies. Retrieved data allowed meta-analysis on 4 registries for total malignancy, and 3 for NMSC (Fig. 1). LTE studies were not pooled.

Registry data

Among the 12 selected studies from registries (21, 29, 31-40), 9 compared the risk of malignancy for RA patients receiving anti-TNF therapy with those receiving synthetic DMARDs (control group) (21, 31-38), and 3 compared patients receiving anti-TNF therapy with the general population (29, 39, 40) ((21) compared both). Registries details are in Tables I and II.

Of the 9 studies comparing the risk with a DMARD-treated group, 3 studies investigated only skin cancer (36, 37, 38), and in 2 other studies (31, 33), lack of information prevented calculating an OR, and their data were not pooled

Table I. Risk of total malignancies and NMSC in studies of anti-TNF *versus* synthetic DMARD therapy from registries.

Author, year, reference	Population, Type of biologic	Characteristics of patient		Cases of cancer (N, PY)		Risk estimate of total malignancy [95% CI]	Additional risk estimates [95% CI]
		Anti-TNF group	DMARD group	Anti-TNF group	DMARD Group		
Askling, 2009 (34)	Swedish registry ARTIS ETA, INF, ADA	25 693 PY 6604 patients disease duration: 10.6 years	23 558 PY starting MTX <i>with NMSC</i>	240 9.34/1000 PY <i>with NMSC</i>	260 11/1000 PY	RR = 0.99 [0.79-1.24]	
Wolfe, 2007 (31)	US National Data Bank for Rheumatic Disease ETA, INF, ADA and ANA	6682 patients* (319 ANA)	6634 patients* under DMARD	231 (6 in anakinra treated patients) <i>without NMSC</i>	306 <i>without NMSC</i>	OR = 1 [0.8-1.2]	Solid cancer OR=1 [0.8-1.2] NMSC OR=1.5 [1.2-1.8] Melanoma OR=2.3 [0.9-5.4] Breast cancer OR=0.9 [0.5-1.3] Lung cancer OR=1.1 [0.7-1.8]
Setogouchi, 2006 (32)	2 American states and 1 Canadian RA > 65 years old ETA, INF, and ANA	2940 PY 1152 patients (28 ANA)	30300 PY 7306 patients under MTX	57 19.4/1000 PY <i>without NMSC</i>	646 21.3/1000 PY <i>without NMSC</i>	HR = 1 [0.75-1.34]	Solid cancer HR=0.92 [0.67-1.26]
Strangfeld, 2010 (21)	German registry RABBIT ETA, INF, ADA and ANA	8762 PY 4493 patients (77 ANA) Disease duration 9 years [5-17] Follow-up duration: 2.4 years [1.4-3.1]	3571 PY under DMARD Disease duration: 6 years [2.5-12] Follow-up duration: 2.5 years [1.3-2.3]	44 5/1000 PY <i>without BCC</i>	30 8.4/1000 PY <i>without BCC</i>	HR = 0.61 [0.39-0.97]	
Carmona, 2007 (35)	Spanish cohort BIOBADASER	2868 PY 4459 patients	2433 PY under DMARD	3.82/1000PY	11.03/1000 PY	OR = 0.4 [0.20-0.83]	
Gibofsky, 2009 (33)	American registry RADIUS ETA	3273 PY	NA	37 11/1000 PY	NA	RR = 0.7	
Mercer, 2009 (36)	BSRBR	41 716 PY	9058 PY	NA	NA		NMSC HR = 1.7 [0.9-3.4] (patients without prior NMSC)
Askling, 2009 (37)	Swedish registry ARTIS ETA, INF, ADA	6604 patients	NA	NA	NA		NMSC RR=1.2 [0.8-2]
Greenberg, 2007 (38)	CORRONA registry	8690 PY	6805 PY	NA	NA		NMSC IRR=1.83 [0.85-3.93]

ETA: etanercept; INF: infliximab; ADA: adalimumab; ANA: anakinra; DMARD: disease-modifying anti-rheumatic drugs; PY: patient-years; MTX: methotrexate; NMSC: non-melanoma skin cancer; BCC: basal cell skin cancer; RR: relative risk, OR: odds ratio, HR: hazard ratio, IRR: incidence rate ratio; 95% CI: 95% confidence interval, NA: not available. *In the Wolfe study, PY was not available.

in the meta-analysis. Consequently, our meta-analysis for risk of total malignancy (solid plus haematological cancers) was based on data from 4 registries (21, 32, 34, 35), including 40,128 patient-years (PY) for the anti-TNF- α treatment group and 59,862 PY for the synthetic DMARD treatment group. The pooled OR for malignancy in the anti-TNF group was 0.81 [0.71-0.94], without significant heterogeneity ($\chi^2 = 5.95$, $df=3$, $p=0.11$; $I^2 = 50\%$) (Fig. 2). In 3 registries, some patients received anakinra (319/6,682 patients in the Wolfe study (31), 28/1,152 patients in the Setogouchi study (32) and 77/3,279 patients in the Strangfeld study (21)). Authors excluded all NMSCs in 2 studies (31, 32) and basal-cell skin cancer in the German registry RABBIT (21) for calculating total malignancy.

Moreover, none of the 6 registries with data for total malignancy and more than 45,000 PY for anti-TNF-treated patients revealed an increased risk as compared with synthetic DMARDs (Table I). Wolfe *et al.* (31) calculated an independent risk of different solid neoplasms, and, excluding skin cancers, did not find any cancer with significantly higher risk for anti-TNF-treated patients as compared with control groups (Table I). However, in this study, OR for risk of NMSC and melanoma was 1.5 [1.2-1.8] and 2.3 [0.99-5.4], respectively (31). So we tried to evaluate this risk of NMSC with TNF antagonist in registries with a specific meta-analysis. Finally 1 study (31) and 3 abstracts (36-38) had complete information on NMSC, and compared anti-TNF group with a synthetic

DMARD group. In addition to the study previously mentioned (31), the risk of NMSC in patients treated with TNF antagonist compared with synthetic DMARDs seemed to be higher but was not statistically significant in three other cohorts (adjusted HR=1.7 [0.9-3.4], regarding patients without history of NMSC in the British Biologic Register (BSRBR) (36), RR=1.2 [0.8-2] for SCC in Swedish registry (37), and IRR=1.83 [0.85-3.93] in CORRONA registry (38)). Retrieved data allowed meta-analysis on 3 registries, pooling 76,099 PY treated with TNF antagonist *versus* 346,361 PY treated with synthetic DMARDs. The pooled OR was 0.79 [0.62-1.02], without significant heterogeneity ($\chi^2=3.80$, $df=2$, $p=0.15$; $I^2=47\%$) (Fig. 3). Four registries (21, 29, 39, 40) com-

Table II. Risk of malignancies of patients receiving anti-TNF therapy *versus* the general population in registries.

Author, year, reference	Population, type of biologic	Characteristics of patients receiving anti-TNF therapy (PY)		SIR* Anti-TNF group [95% CI]	SIR* control population [95% CI]
		Number (PY)	Follow-up duration		
Askling, 2005 (40)	Swedish registry ETA, INF, ADA	9715	2.3 (0-4) years	Solid 0.9 [0.7-1.2] Lung 1.8 [0.9-3.3] SCC 3.6 [1.8-6.5] Melanoma 0.3 [0.0-1.8]	RA all treatments (biologics and non-biologics DMARD) Solid 1.05 [1.01-1.08] Lung 1.48 [1.33-1.65] Scc 1.66 [1.5-1.84] Melanoma 1.19 [0.99-1.42]
Geborek, 2005 (29)	South Sweden Registry ETA, INF, ADA	1603	2.1 (1.3-3.1) years	Total 1.1 [0.6-1.8] Smoking related** 2.2 [0.7-5.1] Other solid 0.5 [0.2-1.2]	RA without biologics Total 1.4 [1.1-1.8] Smoking related** 2.5 [1.5-3.8] other solid 1.2 [0.8-1.6]
Strangfeld, 2010 (21)	German registry RABBIT ETA, INF, ADA and ANA	8762	2.4 [1.4-3.1] years	Total 0.74 [0.54-1]	RA treated with DMARD Total 1.02 [0.68-1.45]
Pay, 2008 (39)	Turkish observatory ETA, INF, ADA	1145	NA	Total 1.36 [0.68-2.43]	

TNF: tumour necrosis factor; PY: patient-years; RA: rheumatoid arthritis; SCC: squamous cell carcinoma; ETA: etanercept; INF: infliximab; ADA: adalimumab; ANA: anakinra; DMARD: disease-modifying anti-rheumatic drug; NA: not available. *SIR: standardised incidence ratio (calculated vs. general population). **Smoking-related cancers: upper gastrointestinal tract, airway, urinary tract.

pared the risk of cancer for anti-TNF-treated patients (21, 225 PY) with that of the general population (Table II). For 3 of these registries (21, 29, 39), the SIR for risk of total malignancy was not significantly higher than 1 and ranged from 0.74 to 1.36. The SIR for risk of solid cancer in the Askling study (40) was 0.9 [0.7–1.2]. In this study, SCC was the only solid neoplasm with an increased risk *versus* the general population (SIR=3.6 [1.8–6.5]) (Table II).

Long-term extension studies

LTE studies allowed for comparison *versus* the general population only. We found a SIR for malignancy in 4 studies (41–44), pooling long-term follow-up data for extension-phase and open-label studies for adalimumab (44) and etanercept (41–43) (Table III). One study compared the specific risk of SCC (45). We found no increase in the incidence of total malignancy (calculated SIRs ranging from 0.81 to 1.07). A recent analysis of data for 10,495 PY in North America and Europe, with early RA (disease duration of less than 3 years, failure of one or more synthetic DMARDs), who agreed to benefit from etanercept in an open-label phase, did not report an increased risk of cancer (SIR=1.00

[0.8–1.23]), with a median follow up of 5.1 years (41).

In the long-term extension of 19 RCTs of adalimumab (18,284 PY), no solid cancer had a SIR significantly greater than 1 (44) (Table III). Nevertheless, the SIR for SCC and basal-cell carcinoma was 1.97 [1.34–2.80] and 1.24 [1.01–1.51], respectively (44).

Lebwohl *et al.* (45) specifically studied the risk of SCC for 4,252 PY with exposure to etanercept in RCTs and long-term follow-up studies. Patients were followed for an average of 2.1 years. Four cases of SCC were observed in RCTs, as compared with 13.1 and 5.9 expected cases, respectively, in Arizona and Minnesota registers. With up to 5-year follow-up 25 cases were observed in the follow-up studies, as compared with 836 and 367 cases expected in the Arizona and Minnesota registers, respectively.

Discussion

Due to its physiopathology involving immunologic disorders, relation between RA and carcinogenesis is evoked for many years. Several authors evaluated risk of malignancy in RA comparing with the general population (20, 31, 40), and found conflicting results. In fact it seems to be difficult to

evaluate the specific cancer risk in RA, as patients have always an immune-modulating treatment, which could increase the risk of malignancy. For example, in an Australian RA cohort, it was recently found an increased risk of solid cancer with methotrexate, in 4,145 PY *versus* the general population (SIR=1.5 [95% CI 1.2–1.9]) (46).

The treatment of RA was based on DMARDs, in association with corticosteroids until recently (47, 48). However, TNF- α antagonists have become a cornerstone in the treatment of RA, and the question about a potential risk of cancer with these therapies remains a major concern for patients and providers. As these treatments are widely used for ten years in RA, many cohorts are available and may provide conflicting results regarding their safety. Our systematic review of the literature, based on 2 types of studies commonly used for treatments follow up, and supported by meta-analysis, allowed us for an exhaustive view of the risk of malignancy in RA patients receiving TNF blockers.

Information differed depending on the studies. If data extracted from RCTs enables a strict comparison with treatment reference, those studies are very

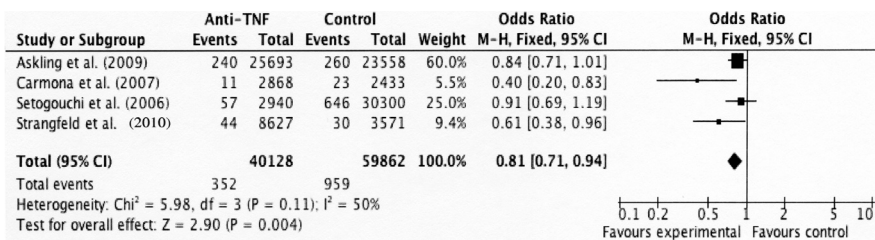


Fig. 2. Risk estimates of total malignancies reported in registries of rheumatoid arthritis (RA) patients receiving tumour necrosis factor (TNF) inhibitors *versus* synthetic disease-modifying anti-rheumatic drugs.

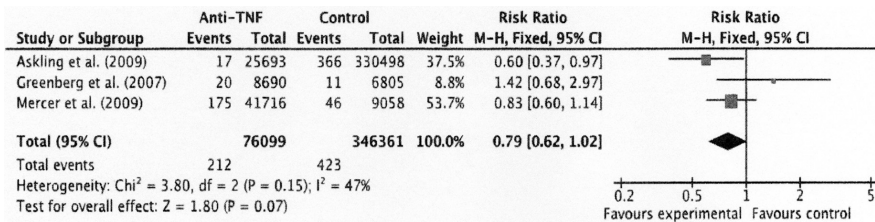


Fig. 3. Risk estimates of NMSC reported in registries of rheumatoid arthritis (RA) patients receiving tumour necrosis factor (TNF) inhibitors *versus* synthetic disease-modifying anti-rheumatic drugs.

short follow up, which is an important limitation for evaluation of malignancy. Thus, we decided to focus the search on LTE studies, which allow for longer follow-up, and registries, which allow for pooling data for a large number of patients and may reveal uncommon adverse effects. Obtaining a view of these two types of data is important to have a real idea of the risk of malignancy with anti-TNF treatment.

The debate on the risk of cancer in RA patients receiving TNF antagonists began in 2006 with the Bongartz *et al.* meta-analysis (24). This study found an increased risk of total malignancy

from RCTs of adalimumab and infliximab in RA. However, this study had several limitations: neoplasms included lymphomas, data were limited to 1-year follow-up, and patients were heterogeneous in included studies. Many authors criticised this analysis and its method, and published comments with new analyses did not reveal exactly similar results (25, 26).

Recently, results of 2 meta-analysis of RCTs were reassuring. Leombruno *et al.* (28) analysed 17 RCTs of 3 anti-TNF therapies *versus* DMARDs. The OR was 1.34 [0.75–2.39] for total malignancy and 1.31 [0.69–2.48] for solid

malignancy (including melanoma). The meta-analysis by Bongartz *et al.* (27) was based on 9 RCTs comparing etanercept and synthetic DMARD or placebo. The HR for total malignancy was 1.84 [0.79–4.28] and 1.86 [0.62–5.59] with and without NMSC, respectively.

However, even by pooling data in a meta-analysis, RCTs are limited in assessing uncommon adverse effects such as cancer because of their short follow-up and small size of the different groups.

LTE studies are of interest in detecting malignancies because of the longer exposure to treatment, but have an understandable channelling bias, mostly following patients who have responded favourably to a treatment. We could retrieve data from long-term studies of adalimumab and etanercept. In these studies, some patients received TNF antagonists for more than 5 years. Of course, these studies had no control treatment group and compared the risk of cancer *versus* the general population, with SIR calculation. These results interpretation may be difficult as SIR are sometimes increased in RA population, regardless the treatment. However, all retrieved LTE studies had the same conclusion: even *versus* the general population, the risk of total cancer was not increased in RA patients receiving anti-TNF therapy. The same trend was found in a recent LTE study of etanercept in 2212 PY with RA (49). The only caution was in terms of the risk of

Table III. Risk of malignancy for patients receiving TNF antagonist *versus* the general population in long-term extension studies.

Author, year, reference	Type of study and biologic	Characteristics of patient in studies				SIR for total malignancy (without NMSC)	Other results (SIR)
		Number	Age (years old)	Sex ratio (female)	Disease duration (years)		
Burmester 2009 (44)	19 extension and open-label studies ADA	18 284 PY 12345 patients	53.8	79.1%	10.6	SIR 0.81 [0.68-0.95]	Melanoma 1.56 [0.74-2.86] Scc 1.97 [1.34-2.80] Bcc 1.24 [1.01-1.51]
Moreland 2006 (42)	7 extension studies ETA	3 199 PY 581 patients	52 (18-86)	80%	12 (0-58)	SIR 1.07 [0.72-1.53]	Scc 4 observed (4 expected) Bcc 11 observed (8 expected)
Klareskog 2006 (43)	Open-label study ETA	1 498 549 patients	53	79%	7.4	SIR 0.84 [0.42-1.51]	
Klareskog 2009 (41)	Open-label study ETA	10 495	NA	NA	NA	SIR 1.00 [0.8-1.23]	

TNF: tumour necrosis factor; PY: patient-years; SCC: squamous cell carcinoma; Bcc: basal cell carcinoma; NMSC: non-melanoma skin cancers; ADA: adalimumab; ETA: etanercept; NA: not available, *SIR: standardised incidence ratio (calculated *vs.* general population).

NMSC, which was found increased in one study (44).

Registries are of interest for evaluating carcinogenic risk because of the long duration of treatment exposure and patient follow-up. Moreover, they seem to be the best studies to reflect real practice. The limitations of these studies are the possibility of concomitant immunosuppressive treatment and the risk of missing information (prior treatment with potential effect on carcinogenesis, patients' history). Furthermore, usually adverse effects in such studies are self-reported. Data from different studies based on registries from different countries were published but never pooled. Although recommendations and local practices may be different throughout these countries, all the registry studies we pooled were on RA populations in North America or Europe, and these RA cohorts had some similarities: age 55–60 years old (with the exception of the Setogouchi study (32)), similar sex ratio, nearly 10 year disease duration, and frequent prior synthetic DMARD treatment. We concluded that pooling them was acceptable, and did not find statistical heterogeneity. To pool the different results from registries, we had to calculate an unadjusted OR for the risk of total malignancy. Data from the Wolfe (31) and Gibofsky (33) studies could not be pooled because of the lack of information (PY in each group). This limitation was of course an important bias for NMSC risk evaluation as the Wolfe study (31) was the only one with a significant higher risk in the anti-TNF group. We had problems pooling data for NMSC: some studies included NMSC in their results, others excluded them, and one study lacked information. Moreover, in 2 studies (21, 32) included in our meta-analysis, few patients received anakinra in the TNF antagonist group.

However, data from each registry are reassuring. Even if patient follow up is only about 3 or 4 years of observations (not clearly defined in different studies), no study recorded an increase in total or solid malignancy with TNF antagonists, as compared with patients receiving synthetic DMARDs or the general population. Our meta-analysis

confirmed this trend, and for the first time, our pooled OR might even suggest a protective effect. Some explanation could be proposed. In a Swedish cohort, Baecklund recently demonstrated that the incidence of lymphoma in RA seems to be linked with disease activity (20). We can suppose a similar mechanism for the risk of total malignancy, and maybe TNF inhibitors, decreasing disease activity, could decrease incidence of malignancy.

In order to corroborate our results, we could mention other cohorts which found that all-cause mortality was not greater than expected in RA patients receiving TNF antagonists (35). Moreover the incidence of cancer is also linked to the risk of recurrence. Some registry studies evaluated this risk of cancer recurrence. For example it was evaluated in 293 patients from a cohort of 14,000 British patients (50). In total, 177 and 117 patients receiving anti-TNF- α and DMARDs, respectively, had a history of malignancy, which mainly occurred in the decade before the biologic prescription. The incidence of malignancy was 25.3/1,000 PY for the anti-TNF-treated group and 38.3/1,000 PY for the DMARD group. The age and sex-adjusted OR was 0.58 [0.23–1.43]. But time between the previous cancer and the start of follow-up was different between the two groups. The same trend was found in the RABBIT registry (21), but the recurrence rate was slightly higher for the anti-TNF treated group (45.5/1,000 PY *versus* 31.4/1,000 PY for the DMARD group) with an incidence rate ratio of 1.4 [0.5–5.5]. The specific risk of solid cancer was calculated for only 2 cohorts: the OR was 1 [0.8–1.2] for the Wolfe study (31), and the HR was 0.92 [0.67–1.26] for the Setogouchi study (32).

Askling *et al.* (34) did not find an increased risk of cancer with treatment exposure. Moreover, Setogouchi *et al.* did not reveal an increase in malignancy with anti-TNF treatment in an older RA population (32).

The only sign of malignancy, as in LTE studies, was related to skin cancers, especially NMSCs, with an increased risk found statistically significant or nearly significant in 2 registries comparing

synthetic DMARDs (31, 36) and in 1 registry comparing the general population (40). However, in this latter study (40), the SIR for SCC was also elevated in the total RA population. Chakravarty *et al.* also found a higher risk of NMSC in RA, regardless the treatment, as compared with a control patient group with osteoarthritis (HR=1.19 [1.01–1.41]) (51). This finding was observed in a recent review of cutaneous malignancy with immuno-modulating treatment (52). That is why it is difficult to evaluate the role of TNF antagonist in risk of NMSC. Our specific meta-analysis of registries did not find an increased risk of NMSC with TNF antagonist *versus* DMARD. This result is conflicting with a recent report of Askling *et al.* who found an increased risk of NMSC with TNF antagonist pooling adalimumab, infliximab and etanercept RCTs data in RA and other diseases (HR=2.02 [1.11–3.95] 95% CI) (53). In order to have an exhaustive view authors used in this study a specific method reporting patient level data.

Besides this specific risk of NMSC, the absence of increased risk of neoplasms with TNF antagonist treatment seems to be a general trend, either from LTE studies or registries.

In summary, our systematic review of literature is reassuring, because no registry or long-term extension studies found an increased risk of total malignancy and of solid cancers with anti-TNF therapy in RA, either as compared with synthetic DMARDs or the general population. This observation is confirmed by our meta-analysis of registries, pooling a great number of patients. Even if our meta-analysis did not conclude to an elevated risk of NMSC with anti-TNF, because of the frequent use of these treatments, strict selection of patients and careful monitoring remain mandatory.

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