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Biologic Treatment of Rheumatoid Arthritis and the Risk of Malignancy

Analyses From a Large US Observational Study

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Objective. **Induction of malignancy is a major concern when rheumatoid arthritis (RA) is treated with biologic therapy. A meta-analysis of RA biologic clinical trials found a general increased risk of malignancy, but this risk was not found in a large observational study. We undertook this study to assess the risk of malignancy among biologic-treated patients in a large US observational database.**

Methods. **We studied incident cases of cancer among 13,001 patients during ~49,000 patient-years of observation in the years 1998–2005. Cancer rates were compared with population rates using the US National Cancer Institute SEER (Surveillance, Epidemiology, and End-Results) database. Assessment of the risk of biologic therapy utilized conditional logistic regression to calculate odds ratios (ORs) as estimates of the relative risk, further adjusted for 6 confounders: age, sex, education level, smoking history, RA severity, and prednisone use.**

Results. **Biologic exposure was 49%. There were 623 incident cases of nonmelanotic skin cancer and 537 other cancers. The standardized incidence ratios and 95% confidence intervals (95% CIs) compared with SEER data were as follows: all cancers 1.0 (1.0–1.1), breast 0.8 (0.6–0.9), colon 0.5 (0.4–0.6), lung 1.2 (1.0–1.4), lymphoma 1.7 (1.3–2.2). Biologics were associated with an increased risk of nonmelanotic skin cancer (OR 1.5, 95% CI 1.2–1.8) and melanoma (OR 2.3, 95% CI 0.9–5.4). No other malignancy was associated with biologic use; the OR (overall risk) of any cancer was 1.0 (95% CI 0.8–1.2).**

Conclusion. **Biologic therapy is associated with increased risk for skin cancers, but not for solid tumors or lymphoproliferative malignancies. These associations were consistent across different biologic therapies.**

The association of rheumatoid arthritis (RA) and cancer is an issue of continuing interest, made more important by possible causal links between RA and cancer as well as between RA treatment and cancer. Epidemiologic studies have generally demonstrated that hematopoietic, lung, and skin cancers are increased in RA, while breast and colon cancers are decreased, and that there is a very slight overall increase in all cancers (1–4). In addition, evidence has accumulated that RA disease activity is associated with the risk of lymphoma (5–8).

Immunosuppression increases cancer rates generally, as evidenced by data from renal transplantation (9–12). In RA, treatment with cyclophosphamide is associated with increased risk of malignancy (13). Evidence is equivocal with respect to azathioprine (14,15). Methotrexate has been linked to malignancy as well (16–18), and discontinuation of methotrexate has been followed by disappearance of lymphoma in some patients ("reversible lymphoma") (17,19). However, no epidemiologic studies have found an increase in lymphoma in methotrexate-treated patients beyond what is expected in RA (20).

Although its mechanism of action is substantially different from that of the immunosuppressive drugs

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noted above, biologic therapy results in profound immunomodulation, and there are long-term concerns regarding the risk of cancer following treatment with biologic therapies. These concerns were underscored by a recent meta-analysis of the risk of malignancy in patients treated with infliximab or adalimumab in randomized controlled trials (21). That study found that the pooled odds ratio (OR) for malignancy in biologic- versus non–biologic-treated patients in randomized controlled trials was 3.3 (95% confidence interval [95% CI] 1.2–9.1). A followup report indicated an OR of 2.02 (95% CI 0.95–4.29) when additional trial data were added (22).

Observational studies have addressed the risk of malignancy in persons treated with biologics. Askling et al used the Swedish inpatient registry cited above (2,3) to compare 4,160 tumor necrosis factor (TNF) antagonist–treated patients with 53,067 patients in the inpatient registry. They found that cancer risks in treated patients were "largely similar to those of other patients with RA" and that "the pattern of patients treated with TNF antagonists mirrors those of other contemporary as well as historic RA cohorts" (2).

Geborek et al (23) studied 757 patients treated with etanercept or infliximab between February 1999 and December 2002, along with 800 patients who received conventional antirheumatic treatment, as a comparison cohort. Although they found no increase in solid tumors in anti-TNF– versus non–anti-TNF–treated patients, the investigators identified 5 lymphomas among 757 anti-TNF–treated RA patients (1,603 person-years). Compared with a non–anti-TNF–treated cohort, the relative risk of lymphoma in anti-TNF–treated patients was 4.9 (95% CI 0.9–26.2). In an accompanying editorial, Franklin et al (24) considered methodologic problems with this report, including the possibility of confounding by indication, latency, and a low rate of lymphoma in the control population.

In the present report, we first describe the rates and risks of malignancy in RA, and then we try to resolve the issues raised by the meta-analysis. In contrast to the 2 observational studies cited above, we investigated the risk of malignancy conferred by biologic therapy in a large time-matched contemporary cohort of 13,001 patients with RA, 49% of whom were exposed to biologic therapy.

PATIENTS AND METHODS

Participants were members of the US National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes who completed semiannual questionnaires in the period 1998 through 2005. NDB participants are recruited on an ongoing basis from the practices of US rheumatologists and are followed up prospectively with semiannual, detailed, 28-page questionnaires, as previously described (25–29). The diagnosis of RA was made by the patients' rheumatologists.

At each semiannual questionnaire assessment, we recorded demographic, disease severity, treatment, and malignancy variables. Patients reported functional status using the Health Assessment Questionnaire (HAQ) (30,31). We determined pain, global severity, and fatigue by visual analog scales (VAS) (32). The VAS measure 21 points from 0 to 10 at 0.5-unit intervals. To assess RA activity, we computed the Patient Activity Scale by multiplying the HAQ score by 3.33 and then dividing the sum of the VAS pain and global scores and rescaled HAQ score by 3. This yields a 0–10 scale with good psychometric properties (33).

At enrollment, participants reported all previous RA medication use. Thereafter, they reported all medication use and timing of use in the previous 6 months. Participants were categorized as having been treated with a biologic agent if they had ever used infliximab, etanercept, adalimumab, or anakinra. For analysis of malignancy risk, only biologic agents used prior to identification of the malignancy were counted as biologic treatments. Approximately 58% of participants who had received infliximab were enrolled in the NDB as part of an infliximab safety registry.

Case identification. The determination of malignancy was based on a formal, written protocol and standardized assessment questionnaires. Patients are contacted by specially trained interviewers whose work is periodically reviewed according to written quality control procedures. In the first step of cancer determination we obtain a report of malignancy, and in the second step we validate the report. Initial reports almost always come from the patient, except in cases when the patient is too ill, and in such instances the initial report may come from a family member or friend.

The question on the NDB semiannual questionnaire that addresses malignancy is as follows (using 2006 as an example date): "Between July 1, 2006 and December 31, 2006 were you told that you had any kind of cancer or malignancy? Yes No. (Please list ALL of the types of cancer diagnosed between July and December on the lines below. For example: leukemia, lymphoma, lung, skin, breast, etc.)."

Following the initial patient report, the NDB conducts a detailed telephone interview with each patient (using a standardized form) and immediately thereafter sends for hospital or medical records. If we cannot contact the patient by telephone, we mail a detailed cancer form for him/her to complete. The interview/form requests specific information about cancer type, dates of cancer diagnosis, type of and response to treatment, reoccurrence, other cancers, and name and address of oncologist. Hospital records are requested for all hospitalizations, and physicians are contacted as necessary.

To determine preexisting malignancy, we make use of the above information. In addition, at enrollment into the NDB, all patients are asked the following question from the NDB enrollment questionnaire: "Have you ever been told that you had any kind of cancer or malignancy? If yes, please list all of the types of cancer that you have ever had, and the year each was diagnosed. For example: leukemia, lymphoma, lung, skin,

breast, etc." Incomplete answers are followed up with a telephone contact.

We also searched the National Death Index (34) annually from 1998 through 2004 and also received reports of deaths from family and friends. Cancers identified in death records within 6 months of final patient participation were accepted as cases. In cases of nonmelanotic skin cancers where there was no hospitalization record and medical confirmation was difficult, patient self-report was accepted after a detailed patient interview.

Exclusions. Analysis of NDB data indicate that there is an ~50% reduction in cancers reported in the patients' first phase (6-month period) in the NDB. Therefore, for the purposes of this study we excluded the initial questionnaire from analysis, because patients with recently diagnosed cancers were less likely to enroll in the NDB. In effect, this required every patient to have 1 cancer-free phase before study participation and at least 2 observations (phases of participation). For each specific cancer, we excluded patients with that preexisting cancer from the specific analysis of that cancer. To control for the potential bias associated with delayed discovery of cancer by the NDB (35), we excluded data from the most recent 6-month assessment period, the second half of 2005.

Statistical analysis. To determine whether the use of biologic therapies influenced the risk of cancer, we used conditional logistic regression and a series of baseline covariates. Because patients entered and left the study at different times and had potential differences in severity according to time, and because treatments became available at different calendar times, we used entry phase and exit phase as a conditioning variable and performed conditional logistic regression to calculate ORs as estimates of the relative risk of various cancers (incidence density ratios). Phases represent consecutive 6-month assessment periods beginning in 1998. Patients may enter the study in any 6-month period (except the last) and exit in any 6-month period (except the first). In these analyses, 140 unique phase-based entry/exit groups were identified and used as the conditioning variable. ORs are reported with 95% CIs. *P* values less than or equal to 0.05 were considered significant.

Conditional logistic regression excludes patients in strata where all subjects have no cancer or all subjects have cancer. Therefore, the number of subjects in these analyses is less than the total number of subjects used to calculate incidence rate densities. In Table 1, we report on the total number of subjects analyzed by conditional logistic regression of all cancers (n = 13,001), which is less than the total number of participants analyzed in the calculation of incidence rate densities (n = 13,869) (Table 2). In addition, the number of subjects analyzed must vary, of necessity, among the different cancers analyzed (Tables 3 and 4).

In addition to entry and exit phase as conditioning variables, we included 6 factors as an a priori set of confounders in all models. The included factors were age, sex, education level, smoking history, Patient Activity Scale, and prednisone use at initial assessment. Patient Activity Scale and prednisone use are measures of RA activity/severity. The other variables are known to be associated with risk of cancer.

For each cancer, we then tested whether any biologic use (ever received biologic therapy) (Table 3) and/or specific biologic agents (Table 4) were/was associated with subsequent cancer. In addition, for each biologic variable, we created a 4-level categorical variable based on quartiles of treatment exposure time to test whether duration of therapy was associated with cancer risk. The 4 categories of time quartiles were 0 years, >0 years to 2 years, >2 years to 4 years, and >4 years. To summarize these data in an intelligible way rather than presenting the effect of duration in the 4 time periods for every cancer, we used the summary trend test (*P* value for trend) (Table 3). In analyses of specific biologic drugs, all biologic therapies were entered into the model simultaneously. Individual analyses for adalimumab and anakinra were not reported separately, because the number of patients receiving these therapies was insufficient for meaningful analyses.

To determine expected rates of specific cancers, we used the US SEER (Surveillance, Epidemiology, and End-Results) database as a comparison population (36). The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the US. The SEER Program currently collects and publishes cancer incidence and survival data from population-based cancer registries covering ~26% of the US population. We used age and sex categories from the SEER database to determine the standardized incidence ratio (SIR) for each cancer studied in the RA sample compared with the US population. Estimates where there are fewer than 20 cases are unstable, and inference from such cases is problematic regardless of statistical significance.

Table 1. Demographic and clinical characteristics of the study participants (n = 13,001) at first observation*

Age, mean ± SD (median) years	58.5 ± 13.1 (58.8)
Male, %	22.0
Years of education, %	
0–8	2.8
>8–11	8.4
12	37.8
13–15	25.8
≥16	25.5
Ethnic origin, %	
White, not of Hispanic origin	92.5
Black, not of Hispanic origin	3.9
Asian or Pacific Islander	1.0
American Indian or Alaskan Native	0.8
Hispanic	1.9
Ever smoked, %	56.4
Disease duration, mean ± SD (median) years	16.7 ± 12.7 (14.5)
HAQ score, 0–3, mean ± SD (median)	1.1 ± 0.7 (1.1)
First Patient Activity Scale score, 0–10, mean ± SD (median)	3.7 ± 2.2 (3.6)
Treatment, %	
Prednisone	45.6
MTX	56.9
Leflunomide	18.7
Sulfasalazine	9.4
HCQ	25.2
Infliximab	19.9
Etanercept	7.6
Adalimumab	0.4
Anakinra	0.3

* HAQ = Health Assessment Questionnaire; MTX = methotrexate; HCQ = hydroxychloroquine.

Table 2. Rates of malignancy among 13,869 study participants with rheumatoid arthritis*

Cancer	Cases	Exposure, patient-years	Crude rate per 100,000 patient-years (95% CI)	SIR (95% CI)†
All†	543	41,912	1,295.6 (1,188.9–1,409.3)	1.0 (1.0–1.1)
Bladder	20	49,021	40.8 (24.9–63.0)	0.8 (0.5–1.0)
Bone	3	49,145	6.1 (1.3–17.8)	5.7 (2.1–14.6)
Brain	1	49,166	2.0 (0.1–11.1)	0.2 (0.0–0.9)
Breast	102	47,848	213.2 (173.8–258.8)	0.8 (0.6–0.9)
Cervix	4	48,582	8.2 (3.1–21.9)	0.8 (0.4–1.9)
Colon	37	48,870	75.7 (53.3–104.4)	0.5 (0.4–0.6)
Endocrine	1	49,156	2.0 (0.1–11.3)	0.1 (0.02–0.6)
Esophagus	10	49,167	20.3 (9.8–37.4)	1.8 (1.1–3.1)
Gall bladder	1	49,170	2.0 (0.1–11.1)	2.0 (0.3–14.4)
Head and neck	5	49,171	10.2 (3.3–23.7)	0.3 (0.2–0.7)
Hodgkin's	4	49,116	8.1 (2.2–20.8)	3.0 (1.3–6.8)
Kidney	7	49,101	14.3 (5.7–29.4)	0.5 (0.2–0.9)
Leukemia	24	49,118	48.9 (31.3–72.7)	1.7 (1.2–2.4)
Liver	6	49,155	12.2 (4.5–26.6)	0.9 (0.5–1.8)
Lymphoma	45	49,085	91.7 (66.9–122.7)	1.7 (1.3–2.2)
Lung	112	49,037	228.8 (188.1–274.8)	1.2 (1.0–1.4)
Melanoma	32	48,795	65.6 (44.9–92.6)	1.7 (1.3–2.3)
Non-Hodgkin's	42	49,103	85.5 (61.6–115.6)	1.7 (1.3–2.2)
Ovary	7	48,948	14.3 (5.7–29.5)	0.5 (0.3–0.9)
Pancreas	12	49,175	24.4 (12.6–42.6)	0.7 (0.4–1.1)
Prostate	56	48,732	114.9 (86.8–149.2)	0.8 (0.6–1.0)
Skin‡	624	46,494	1,342.1 (1,238.8–1,451.7)	NA
Soft tissue	4	49,171	8.1 (3.0–21.6)	1.4 (0.6–3.2)
Solid§	473	41,763	1,132.6 (1,035.0–1,239.4)	1.0 (0.9–1.0)
Stomach	4	49,147	8.1 (2.2–20.8)	0.4 (0.2–0.9)
Testicular	1	49,172	2.0 (0.1–11.3)	2.0 (0.3–14.4)
Uterus	7	48,520	14.4 (5.8–29.7)	0.3 (0.1–0.4)
Vagina	2	49,169	4.1 (0.5–14.7)	2.7 (0.8–8.6)

* 95% CI = 95% confidence interval; SIR = standardized incidence ratio; NA = not available.
† Excludes nonmelanoma skin malignancies.
‡ Excludes melanoma.
§ Excludes lymphoma, leukemia, myeloma, and nonmelanoma skin malignancies.

We conducted a number of sensitivity analyses with respect to the association of biologics with malignancy. In these analyses we eliminated cancer cases discovered only in death records, allowed all data in 2005 to be used, changed the conditional logistic regression grouping variable from phase of entry/exit to year of entry/exit, and allowed patients with fewer than 2 phases to be analyzed. The results of these analyses were not essentially different from those of the study analyses described below and are therefore not reported.

RESULTS

Of the 13,869 RA patients studied for all cancers, 868 were excluded by the conditional logistic regression requirements. The characteristics of the 13,001 remaining patients are shown in Table 1. At the time of entry to the study, the mean ± SD age of participants was 58.5 ± 13.1 years. Men constituted 22.0% of the sample, non-Hispanic whites 92.5%, and college graduates 25.5%. More than half of the patients had a history of smoking (56.4%), and almost half were receiving prednisone (45.6%). The number and percent of patients using biologic therapy during the study were as follows: any therapy 5,257 (40.7%), infliximab 4,277 (33.1%), etanercept 3,011 (23.3%), adalimumab 763 (5.9%), and anakinra 319 (2.5%). The mean duration (range) in years of each treatment was as follows: any therapy 3.0 (0.5–7.8), infliximab 2.9 (0.5–7.8), etanercept 2.7 (0.5–7.7), adalimumab 1.2 (0.5–7.7), and anakinra 1.6 (0.5–3.9).

The rate of malignancy in RA. As shown in Table 2, there was no increase in the overall rate of cancer in participating RA patients compared with SEER data (SIR 1.0, 95% CI 1.0–1.1). A number of malignancies were more common in the RA patient sample than in the SEER database, including lymphoma (SIR 1.7, 95% CI 1.3–2.2) and melanoma (SIR 1.7, 95% CI 1.3–2.3). The lower limit of the 95% CI crossed 1 for lung cancer, resulting in an SIR of 1.2 (95% CI 1.0–1.4). Rates were reduced for breast cancer (SIR 0.8, 95% CI 0.6–0.9) and

Table 3. Association of biologic therapy and subsequent malignancy*

Cancer	Cases	Subjects analyzed	OR (95% CI)†	*P*	*P* for trend‡	Users of biologics
All§	537	12,916	1.0 (0.8–1.2)	0.858	0.678	6,282
Bladder	20	4,687	0.5 (0.1–1.5)	0.197	0.768	1,862
Bone	3	376	0.0 (0–)	0.999	0.999	102
Brain	1	111	¶	¶	¶	44
Breast	102	10,541	0.9 (0.5–1.3)	0.560	0.539	5,196
Colon	37	3,795	0.8 (0.3–1.7)	0.506	0.345	2,503
Endocrine	1	154	¶	¶	¶	66
Esophagus	10	2,374	0.9 (0.2–5.0)	0.907	0.801	1,302
Gall bladder	1	1,099	¶	¶	¶	555
Head and neck	5	926	0.7 (0.1–5.5)	0.757	0.801	378
Hodgkin's	4	696	>1,000 (0–)	0.999	0.038	264
Kidney	7	2,221	1.8 (0.3–9.4)	0.507	0.399	807
Leukemia	24	3,348	1.2 (0.5–3.1)	0.704	0.696	1,367
Liver	6	1,762	0.2 (0.0–2.9)	0.256	0.547	675
Lung	112	8,627	1.1 (0.7–1.8)	0.630	0.737	3,610
Lymphoma	45	5,901	1.0 (0.5–2.0)	0.967	0.462	2,221
Melanoma	32	3,260	2.3 (0.9–5.4)	0.070	0.256	1,394
Non-Hodgkin's	42	5,589	0.7 (0.3–1.5)	0.335	0.183	2,080
Ovary	7	1,416	3.6 (0.6–21.1)	0.153	0.076	587
Pancreas	12	1,857	0.5 (0.1–2.6)	0.440	0.930	481
Prostate	56	7,511	0.9 (0.4–1.9)	0.734	0.189	2,884
Skin#	623	13,584	1.5 (1.2–1.8)	<0.001	0.075	6,597
Soft tissue	4	806	0.3 (0.0–4.8)	0.378	0.998	205
Solid**	467	12,839	1.0 (0.8–1.2)	0.867	0.851	6,238
Stomach	4	806	0.8 (0.1–9.3)	0.891	0.675	1,018
Testicular	1	358	0.0 (0.0–)	0.999	0.999	63
Uterus	7	742	0.0 (0.0–)	0.998	0.993	250
Vagina	2	960	0.6 (0.0–10.3)	0.735	0.470	706

* OR = odds ratio; 95% CI = 95% confidence interval.
† Adjusted for age, sex, education, smoking history, baseline Patient Activity Scale score, and baseline prednisone use.
‡ "Ever received biologic therapy" was replaced by quartiles of biologic time exposure. Mean values are 0, 1.2, 3.0, and 4.7 years.
§ Excludes nonmelanoma skin malignancies.
¶ Indicates nonconvergence of the statistical algorithm due to an insufficient number of cases.
# Excludes melanoma.
** Excludes lymphoma, leukemia, myeloma, and nonmelanoma skin malignancies.

colon cancer (SIR 0.5, 95% CI 0.4–0.6). The upper limit of the 95% CI crossed 1 for bladder cancer (SIR 0.8, 95% CI 0.5–1.0).

The association of biologic therapy and malignancy. In Table 3 the maximum number of patients analyzed was 13,584, and 6,597 of these patients received treatment with biologics. The numbers were slightly smaller when patients with preexisting skin cancer were excluded. In that instance, of 12,916 patients studied, 6,282 had received biologics. When all biologic therapies were considered as a group, the risk of nonmelanotic skin cancer (OR 1.5 [95% CI 1.2–1.8]) and possibly of melanoma (OR 2.3 [95% CI 0.9–5.4], $P = 0.070$) was increased in patients who received biologics (Table 3). However, no other malignancy was significantly associated with biologic use, and the OR for all cancers overall was 1.0 (95% CI 0.8–1.2). The addition of duration of therapy to the model (the next-to-last column in Table 3) did not strengthen positive associations with biologic therapy.

Table 4 extends the analyses to individual biologics. Infliximab (OR 2.6 [95% CI 1.0–6.7], $P = 0.056$) and etanercept (OR 2.4 [95% CI 1.0–5.8], $P = 0.054$) were associated with melanoma. Infliximab (OR 1.7 [95% CI 1.3–2.2], $P < 0.001$) and etanercept (OR 1.2 [95% CI 1.0–1.5], $P = 0.081$) were also associated with non-melanotic skin cancer. No association was noted with any other malignancy.

DISCUSSION

The main finding of this study is the positive association between biologic therapy and skin cancers and the nonassociation of biologic therapy with all other

Table 4. Association of biologic therapies and subsequent malignancy, for malignancies with 20 or more cases in the National Data Bank for Rheumatic Diseases*

Cancer, treatment	Treated cases	Total subjects	Treated subjects	OR (95% CI)†	*P*
All‡					
Infliximab	125	12,916	4,277	1.0 (0.8–1.3)	0.820
Etanercept	93	12,916	3,011	1.0 (0.8–1.3)	0.962
Adalimumab	7	12,916	763	0.7 (0.3–1.6)	0.393
Anakinra	6	12,916	319	0.8 (0.3–1.8)	0.515
Bladder					
Infliximab	2	4,687	1,070	0.4 (0.1–1.8)	0.228
Etanercept	4	4,687	1,037	1.5 (0.4–4.7)	0.513
Adalimumab	0	4,687	253	0.0 (0.0–)	0.991
Anakinra	0	4,687	116	0.0 (0.0–)	0.991
Breast					
Infliximab	22	10,541	3,463	0.9 (0.5–1.7)	0.854
Etanercept	19	10,541	2,571	0.8 (0.5–1.4)	0.505
Adalimumab	4	10,541	658	1.6 (0.5–4.7)	0.387
Anakinra	2	10,541	279	1.1 (0.2–4.6)	0.993
Colon					
Infliximab	7	3,795	614	1.1 (0.4–2.9)	0.787
Etanercept	5	3,795	838	0.7 (0.3–2.0)	0.542
Adalimumab	0	3,795	114	0.0 (0.0–)	0.993
Anakinra	0	3,795	66	0.0 (0.0–)	0.990
Leukemia					
Infliximab	7	3,438	891	0.9 (0.3–2.7)	0.807
Etanercept	4	3,438	708	1.0 (0.3–3.1)	1.000
Adalimumab	0	3,438	95	0.0 (0.0–)	0.993
Anakinra	0	3,438	59	0.0 (0.0–)	0.993
Lung					
Infliximab	30	8,627	2,412	1.2 (0.7–2.1)	0.465
Etanercept	19	8,627	1,808	1.0 (0.6–1.8)	0.877
Adalimumab	0	8,627	335	0.0 (0.0–)	0.990
Anakinra	0	8,627	183	0.0 (0.0–)	0.989
Lymphoma					
Infliximab	12	5,901	1,182	0.9 (0.4–2.1)	0.898
Etanercept	10	5,901	1,313	1.3 (0.6–2.8)	0.460
Adalimumab	1	5,901	251	1.3 (0.2–10.0)	0.826
Anakinra	0	5,901	95	0.0 (0.0–)	0.992
Melanoma					
Infliximab	11	3,260	790	2.6 (1.0–6.7)	0.056
Etanercept	9	3,260	754	2.4 (1.0–5.8)	0.054
Adalimumab	1	3,260	207	0.8 (0.1–6.6)	0.822
Anakinra	2	3,260	77	4.2 (0.9–20.0)	0.075
Non-Hodgkin's					
Infliximab	11	5,589	1,108	1.0 (0.4–2.3)	0.969
Etanercept	7	5,589	1,251	1.0 (0.4–2.1)	0.838
Adalimumab	0	5,589	200	0.0 (0.0–)	0.992
Anakinra	0	5,589	92	0.0 (0.0–)	0.993
Prostate					
Infliximab	6	7,511	1,693	0.5 (0.2–1.5)	0.223
Etanercept	6	7,511	1,579	0.8 (0.3–2.1)	0.642
Adalimumab	0	7,511	341	0.0 (0.0–)	0.996
Anakinra	1	7,511	137	4.0 (0.4–37.4)	0.223
Skin§					
Infliximab	161	13,584	4,430	1.7 (1.3–2.2)	<0.001
Etanercept	126	13,584	3,163	1.2 (1.0–1.5)	0.081
Adalimumab	10	13,584	812	0.9 (0.5–1.8)	0.828
Anakinra	11	13,584	317	1.4 (0.7–2.8)	0.289

* OR = odds ratio; 95% CI = 95% confidence interval.
† Adjusted for age, sex, education, smoking history, baseline Patient Activity Scale score, and baseline prednisone use.
‡ Excludes nonmelanoma skin malignancies.
§ Excludes melanoma.

malignancies. Most malignancies have long latency periods in the absence of immunosuppression. For example, the latency period for lung cancer following cigarette smoking and for breast cancer following cosmic radiation exceeds 15 years (37,38). However, immunosuppression shortens the latency period and increases the range of cancers identified.

Immunosuppressant therapy following renal transplantation in Nordic countries between 1964 and 1986 was associated with excess risks for cancers of the colon, larynx, lung, bladder, prostate, and testis, and with particularly high risk for cancers of the lip, skin (nonmelanoma), kidney, endocrine glands, non-Hodgkin's lymphoma, and cancers of the cervix and vulva-vagina (9). In The Netherlands following renal transplantation, the overall incidence of squamous cell carcinoma was 250 times higher than that in the general Dutch population, and that of basal cell carcinoma was 10 times higher (39). In a study of 35,765 recipients of renal transplants in the US Medicare billing claims database, the above data were confirmed (10). Compared with the incidence of tumors in patients on the waiting list for transplantation in this database, several tumors were more common after transplantation, including nonmelanoma skin cancers (2.6-fold), melanoma (2.2-fold), Hodgkin's lymphoma (2.6-fold), and non-Hodgkin's lymphoma (3.3-fold) (10). Not increased in these analyses were cancers of the lung or breast. Colon cancer was reduced (1.3-fold; $P = 0.086$), and prostate cancer was reduced (1.3-fold). However, the risk of malignancy differs according to the degree of immunosuppression used with transplantation, with the strongest associations occurring in cyclosporine-treated patients (11,12).

Although our data do not show associations between malignancy and biologic therapy, except for skin cancers, the mean and median exposure to biologics was only 3.0 years. It is possible that with increasing time of followup or of exposure, the association between malignancy and biologic therapy would become stronger. However, true associations are regularly seen within this time frame, since posttransplantation studies have shown increased risk after the first year of treatment (9,10).

The data in the current report differ substantially from those in the meta-analysis of randomized clinical trials by Bongartz et al (21). Those authors noted that the pooled OR for malignancy in biologic- versus non–biologic-treated patients in randomized controlled trials was 3.3 (95% CI 1.2–9.1).

There are a number of differences between our study and the meta-analysis. In the meta-analysis, there were 3,493 biologic-treated participants and 1,512 non–biologic-treated control subjects. The individual trial durations ranged between 3 months and 1 year. Data regarding malignancies occurring after the trials were available for 3 of the 9 trials and were reported over an indeterminate period of time. Of the malignancies identified, 23 occurred in adalimumab-treated patients and 12 occurred in infliximab-treated patients (some patients had more than 1 malignancy). Patients treated with etanercept were not studied.

In contrast, adalimumab was infrequently used in our cohort, and adalimumab followup was of short duration. The lack of use in our cohort was a function of the recent release of adalimumab for RA treatment and our exclusion requirements. However, our study included participants treated with etanercept. We identified 125 malignancies in 4,277 infliximab-treated patients and 93 malignancies in 3,011 etanercept-treated patients. The mean duration of followup was 4.1 years (median 3.9 years). Among patients exposed to biologics, the mean and median exposure was 3.0 years. The OR for all malignancies was 1.0 (95% CI 0.8–1.3) for patients treated with biologics. This result is substantially different from the OR of 3.3 (95% CI 1.2–9.1) noted by Bongartz et al (21) in their meta-analysis of clinical trials, and also substantially different from the OR of 2.02 (95% CI 0.95–4.29) obtained by Costenbader et al (22) when these investigators used the same methods described by Bongartz et al to update the results of the meta-analysis (21) with additional trial data.

The meta-analysis report has generated commentary and concerns with respect to whether methodologic issues of case identification might have been an important determinant of the observed results (40). The authors of the meta-analysis report replied to the critique and suggested that "treatment registries will provide widely generalizable results about treatment response" (41). We hope that the current study will provide useful data to illuminate this issue.

The primary limitation of observational studies lies in nonrandom assignment to treatment. If severity of arthritis is related to the outcome of interest and persons with severe arthritis are more likely to be treated with biologics, then outcome is confounded by indication and could be more related to arthritis severity than to treatment. With respect to malignancy, such confounding is known to occur with lymphoma (3,42). However, no other malignancy is known to be associated with RA severity. On that basis we might assume that confound-

ing is not a problem with respect to malignancies other than hematologic malignancies. If we assume the contrary, that malignancies are associated with RA severity and, therefore, with biologic use, we would expect to identify extra malignancies because of this bias. However, we found no such increased risk, even with lymphoma. In that respect our results are strongly concordant with those of the Swedish observational studies (2,3,23).

Observational studies may also have limitations because of time-varying and non–time-varying confounders. For example, the probability of biologic prescription varies over calendar time, as does the severity of RA. Study dropouts are also related to severity and secular trends in access to biologics, for example. We used conditional logistic regression to reduce the effect of these confounders. In addition, in our analyses we controlled for the non–time-varying confounders: age, sex, education level, smoking history, disease activity/severity as measured by the Patient Activity Scale, and baseline use of prednisone.

With regard to cancer risk generally, and without consideration of treatment, population-based studies prior to the time of common use of biologic agents found a number of associations between RA and malignancy. A 1996 report on 20,699 persons with RA in Denmark reported statistically significant risk ratios for malignancies, as follows: lung (1.5), hematopoietic malignancies (1.7), nonmelanotic skin (1.3), breast (0.8), colon (0.8), and all cancers (1.08) (1). Similar results using SIRs were obtained from the Swedish RA inpatient registry of 53,067 patients for the years 1964–2004: lymphoma (1.9), lung (1.5), kidney (1.5), nonmelanotic skin (1.7), colon (0.7), breast (0.8), and all cancers (1.05) (2,3). Significant SIR results from a Scottish registry containing 124,143 patients with a rheumatic condition from 1981 to 1996 were as follows: hematopoietic malignancies (males 2.1, females 1.8), lung (males 1.3, females 1.4), prostate (1.3), and colorectal cancer (males 0.9, females 0.7) (4). The results of our study are generally concordant with those of these studies.

With respect to cancer incidence, however, it is possible that we slightly underestimated incidence, although this does not affect biologic/nonbiologic risk estimates. All cancer data represent various degrees of underreporting. The SEER Program, for example, waits several years to capture corrections and additions before publication (35). Even after a 2-year delay, SEER Program reporting accounts for just 88–97% of the estimated final incidence case counts. For the NDB, reporting delay may come in the delayed identification of recent cases or cases in which the patient dies. Death data in some instances depend upon National Death Index (NDI) data, the public release of which is delayed by ~2 years. Therefore, even if NDB data capture was perfect, it would likely underestimate true rates very slightly in the most recent years.

NDB cancer data may also be incomplete if a participant in whom cancer develops withdraws from the NDB study because of that cancer and the accompanying illness. The NDB conducts exit interviews to capture such cancer events. In addition, the NDB may contact the physician to determine cancer status.

Even with the possible underreporting noted above, the SIRs reported in Table 2 are generally concordant with those in other RA cancer incidence studies. In that respect, we noted increased risks for melanoma, nonmelanotic skin cancer, and lymphoma, and decreased risks for breast and colon cancer. The SIR for lung cancer was 1.2 (95% CI 1.0–1.4) compared with 1.5 in the Danish and Swedish studies (1,2). However, this difference might be attributable to the association between smoking and RA (43,44) and the higher rate of smoking in Europe compared with the US (45). In the Nordic studies the overall cancer SIRs were 1.08 and 1.05 compared with 1.0 in the current (NDB) study.

There are other possible limitations to our study. It is possible that a history of malignancy may affect a physician's decision to prescribe an anti-TNF medication, thus allowing for confounding by indication. In the current study we excluded all patients with a previous history of the specific malignancy under study in order to be able to obtain incident data. However, we did not exclude patients with prior malignancies other than those currently under study. To understand whether this made a difference, we conducted sensitivity analyses in which we excluded all patients with preexisting malignancies. The results were essentially unchanged. For lung cancer, for example, the number of cancers and patients analyzed was 111 instead of 112, and the OR was unchanged from that shown in Table 3. For breast cancer, as an example, the number of cancers was 101 instead of 102, and the OR was unchanged.

Another potential limitation comes from our use of the NDI. A small number of cases reported in the current study were identified using only the NDI. It is possible that this could introduce a bias toward more lethal malignancies and away from finding an effect for nonlethal malignancies, such as skin cancers, breast, colon, prostate, etc. To examine this possibility, we conducted sensitivity analyses by excluding all cancer deaths. The ORs for the association of biologic therapy

with major cancers were as follows: lung 1.2 (95% CI 0.6–2.3), $P = 0.548$; solid tumors 1.0 (95% CI 0.8–1.3), $P = 0.991$; all cancers 1.0 (95% CI 0.8–1.3), $P = 0.764$; skin 1.5 (95% CI 1.2–1.8), $P < 0.001$; melanoma 2.4 (95% CI 1.0–5.9), $P = 0.054$; and breast 0.9 (95% CI 0.6–1.5), $P = 0.697$. Therefore, the exclusion of death data did not result in any real changes to the study results presented in Table 3.

In summary, biologic therapy is associated with increased risk for skin cancers, but not for solid tumors or lymphoproliferative malignancies. These associations are consistent across different biologic therapies.

AUTHOR CONTRIBUTIONS

Dr. Wolfe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Wolfe, Michaud.
Acquisition of data. Wolfe, Michaud.
Analysis and interpretation of data. Wolfe, Michaud.
Manuscript preparation. Wolfe.
Statistical analysis. Wolfe, Michaud.

ROLE OF THE STUDY SPONSOR

The National Data Bank for Rheumatic Diseases has conducted safety registries for Centocor, Sanofi-Aventis, and Bristol-Myers Squibb. By our safety registry contractual agreement with Centocor, the completed manuscript was reviewed by Centocor. No changes to the manuscript were made after their review.

REFERENCES

1. Mellemkjaer L, Linet MS, Gridley G, Frisch M, Moller H, Olsen JH. Rheumatoid arthritis and cancer risk. Eur J Cancer 1996;32A: 1753–7.
2. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1421–6.
3. Askling J, Fored CM, Baecklund E, Brandt L, Backlin C, Ekbom A, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1414–20.
4. Thomas E, Brewster DH, Black RJ, Macfarlane GJ. Risk of malignancy among patients with rheumatic conditions. Int J Cancer 2000;88:497–502.
5. Baecklund E, Ekbom A, Sparen P, Feltelius N, Klareskog L. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. Br Med J 1998;317:180–1.
6. Wolfe F. Inflammatory activity, but not methotrexate or prednisone use predicts non-Hodgkin's lymphoma in rheumatoid arthritis: a 25-year study of 1,767 RA patients [abstract]. Arthritis Rheum 1998;41 Suppl 9:S188.
7. Newkirk MM, Shiroky JB, Johnson N, Danoff D, Isenberg DA, Shustik C, et al. Rheumatic disease patients, prone to Sjögren's syndrome and/or lymphoma, mount an antibody response to BHRF1, the Epstein-Barr viral homologue of BCL-2. Br J Rheumatol 1996;35:1075–81.
8. Van de Rijn M, Cleary ML, Variakojis D, Warnke RA, Chang PP, Kamel OW. Epstein-Barr virus clonality in lymphomas occurring in patients with rheumatoid arthritis. Arthritis Rheum 1996;39: 638–42.
9. Birkeland SA, Storm HH, Lamm LU, Barlow L, Blohme I, Forsberg B, et al. Cancer risk after renal transplantation in the Nordic countries, 1964–1986. Int J Cancer 1995;60:183–9.
10. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant 2004;4:905–13.
11. Jensen P, Hansen S, Moller B, Leivestad T, Pfeffer P, Geiran O, et al. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J Am Acad Dermatol 1999;40(2 Pt 1):177–86.
12. Tremblay F, Fernandes M, Habbab F, deB Edwardes MD, Loertscher R, Meterissian S. Malignancy after renal transplantation: incidence and role of type of immunosuppression. Ann Surg Oncol 2002;9:785–8.
13. Radis CD, Kahl LE, Baker GL, Wasko MC, Cash JM, Gallatin A, et al. Effects of cyclophosphamide on the development of malignancy and on long-term survival of patients with rheumatoid arthritis: a 20-year followup study. Arthritis Rheum 1995;38: 1120–7.
14. Jones M, Symmons D, Finn J, Wolfe F. Does exposure to immunosuppressive therapy increase the 10 year malignancy and mortality risks in rheumatoid arthritis? A matched cohort study. Br J Rheumatol 1996;35:738–45.
15. Silman AJ, Petrie J, Hazleman B, Evans SJ. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. Ann Rheum Dis 1988;47:988–92.
16. Kamel OW, Vanderijn M, Weiss LM, Delzoppo GJ, Hench PK, Robbins BA, et al. Reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis: brief report. N Engl J Med 1993; 328:1317–21.
17. Shiroky JB, Newkirk MM. Reversible lymphomas. N Engl J Med 1993;329:1657–8.
18. Georgescu L, Quinn GC, Schwartzman S, Paget SA. Lymphoma in patients with rheumatoid arthritis: association with the disease state or methotrexate treatment. Semin Arthritis Rheum 1997;26: 794–804.
19. Liote F, Pertuiset E, Cochandpriollet B, Dagay MF, Dombret H, Numeric P, et al. Methotrexate related B lymphoproliferative disease in a patient with rheumatoid arthritis: role of Epstein-Barr virus infection. J Rheumatol 1995;22:1174–8.
20. Mariette X, Cazals-Hatem D, Warszawki J, Liote F, Balandraud N, Sibilia J. Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3-year prospective study in France. Blood 2002;99:3909–15.
21. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275–85.
22. Costenbader KH, Glass R, Cui J, Shadick N. Risk of serious infections and malignancies with anti-TNF antibody therapy in rheumatoid arthritis. JAMA 2006;296:2201–4.
23. Geborek P, Bladstrom A, Turesson C, Gulfe A, Petersson IF, Saxne T, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis 2005;64:699–703.
24. Franklin JP, Symmons DP, Silman AJ. Risk of lymphoma in patients with RA treated with anti-TNFα agents. Ann Rheum Dis 2005;64:657–8.
25. Wolfe F, Michaud K, Anderson J, Urbansky K. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum 2004;50:372–9.

26. Wolfe F, Michaud K. Severe rheumatoid arthritis (RA), worse outcomes, comorbid illness, and sociodemographic disadvantage characterize RA patients with fibromyalgia. J Rheumatol 2004;31: 695–700.
27. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti–tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum 2004;50:1740–51.
28. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med 2004;116:305–11.
29. Michaud K, Messer J, Choi HK, Wolfe F. Direct medical costs and their predictors in patients with rheumatoid arthritis: a 3-year study of 7,527 patients. Arthritis Rheum 2003;48:2750–62.
30. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol 1982;9:789–93.
31. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.
32. Wolfe F, Hawley DJ, Wilson K. The prevalence and meaning of fatigue in rheumatic disease. J Rheumatol 1996;23:1407–17.
33. Wolfe F, Michaud K, Pincus T. A composite disease activity scale for clinical practice, observational studies and clinical trials: the Patient Activity Scale (PAS/PAS-II). J Rheumatol 2005;32: 2410–5.
34. Doody MM, Hayes HM, Bilgrad R. Comparability of national death index plus and standard procedures for determining causes of death in epidemiologic studies. Ann Epidemiol 2001;11:46–50.
35. Clegg LX, Feuer EJ, Midthune DN, Fay MP, Hankey BF. Impact of reporting delay and reporting error on cancer incidence rates and trends. J Natl Cancer Inst 2002;94:1537–45.
36. US Department of Health and Human Services, National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Limited-Use, Nov 2006 Sub (1973–2004), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2007, based on the November 2006 submission.
37. Baldini EH, Strauss GM. Women and lung cancer: waiting to exhale. Chest 1997;112(4 Suppl):229–34S.
38. Rafnsson V, Tulinius H, Jonasson JG, Hrafnkelsson J. Risk of breast cancer in female flight attendants: a population-based study (Iceland). Cancer Causes Control 2001;12:95–101.
39. Hartevelt MM, Bavinck JN, Kootte AM, Vermeer BJ, Vandenbroucke JP. Incidence of skin cancer after renal transplantation in The Netherlands. Transplantation 1990;49:506–9.
40. Dixon W, Silman A. Is there an association between anti-TNF monoclonal antibody therapy in rheumatoid arthritis and risk of malignancy and serious infection? Commentary on the meta-analysis by Bongartz et al. Arthritis Res Ther 2006;8:111.
41. Matteson EL, Bongartz T, Sutton AJ, Buchan I. Response to commentary by Dixon and Silman on the systematic review and meta-analysis by Bongartz et al. Arthritis Res Ther 2006;8:404.
42. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum 2006;54:692–701.
43. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA–DR (shared epitope)–restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38–46.
44. Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. J Rheumatol 2003;30:36–40.
45. Jha P, Ranson MK, Nguyen SN, Yach D. Estimates of global and regional smoking prevalence in 1995, by age and sex. Am J Public Health 2002;92:1002–6.