Review

Does Anti-Tumor Necrosis Factor-α Therapy Affect Risk of Serious Infection and Cancer in Patients with Rheumatoid Arthritis?: A Review of Longterm Data

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ABSTRACT. Given the important role tumor necrosis factor-α (TNF-α) antagonists play in managing rheumatoid arthritis and the concern for safety during longterm therapy, we reviewed the latest evidence regarding longterm risk of infection and malignancy with TNF-α antagonists. Our objective was to provide clinicians with information that can be used to counsel and monitor patients who may be candidates for biologic therapy for rheumatoid arthritis (RA). Risk is examined in the context of background infection and malignancy rates in RA. Randomized controlled trial (RCT) data and observational studies summarizing the risk of infection and/or malignancy in RA and specific risks associated with the use of anti-TNF-α biologic agents (adalimumab, infliximab, and etanercept) were identified through a PubMed search. Overall, patients with RA appear to have an approximately 2-fold increased risk of serious infection compared to the general population and non-RA controls, irrespective of TNF-α antagonist use. Although data on infection rates with TNF-α antagonist use are contradictory, caution is merited. Recent analyses suggest that the risk of infection is highest within the first year. Regarding malignancy risk, RCT and observational data are also conflicting; however, caution is warranted regarding lymphoproliferative cancers in children and adolescents. (First Release May 15 2011; J Rheumatol 2011;38:1552–62; doi:10.3899/jrheum.100995)

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Tumor necrosis factor-α (TNF-α) was the first inflammatory cytokine validated as a therapeutic target in rheumatoid arthritis (RA), and several TNF-α antagonists have since been approved in the United States and Canada. These have shown benefit in RA as monotherapy and in combination with traditional disease-modifying antirheumatic drugs (DMARD) such as methotrexate (MTX). However, while considered safe and well tolerated, the possible increased risk of serious infection and malignancy observed in a meta-analysis of randomized placebo-controlled trials (RCT) with TNF-α antagonists has generated interest in longterm safety risks[1].

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In assessing the magnitude of risk, the effect of background rates of infection and malignancy in RA and other confounding variables such as concomitant therapies (e.g., corticosteroids) has been debated. Moreover, there has been significant interest in how mechanisms of TNF-α neutralization may relate to the observed infection and malignancy risk for each agent. Risk estimates have also varied among RCT or observational studies, partly because of biases inherent in each dataset. Specifically, RCT can establish causal relationships between treatment and an adverse event and can potentially eliminate bias through randomization. However, study entry criteria often exclude high-risk individuals. Short trial duration and small sample sizes can limit the precision of risk estimates, especially when analyzing rare event data. In contrast, observational studies provide risk estimates in nonidealized environments over longer periods of exposure. However, treatment assignment cannot be controlled and any imbalances between treatment and control groups may bias risk estimates.

Over the past few years, several methods have been used to improve estimates regarding risk of infection and malignancy associated with anti-TNF-α agents. Specifically, metaanalyses have been conducted to increase the number of observed events and improve the statistical power of risk estimates from RCT data. Propensity scores have also been

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used for observational datasets to match treatment and control subjects based on covariates that may affect a patient's risk, therefore reducing the effect of potential biases. Previous observational datasets also examined risks associated with anti-TNF-α therapy based on general population comparators, which may overestimate treatment-related risk because of the elevated background risk in RA. While these analyses have been useful for providing initial assessments of risk associated with anti-TNF-α therapy, analyses with anti-TNF-α-naive populations are preferable because the background risk associated with concomitant therapies and the disease process itself may be offset. Newer analyses have emerged that account for these and other factors, helping clarify the magnitude of infection and malignancy risk associated with anti-TNF-α therapies.

The objective of this review is to provide an update on the latest evidence regarding longterm risk of infection and malignancy with TNF-α antagonists. Risk is examined in the context of background infection and malignancy rates in RA, including the biases inherent in both RCT and observational studies. Our review was limited to safety data for adalimumab, etanercept, and infliximab, because of a lack of longterm safety data on newer agents (e.g., certolizumab and golimumab).

MATERIALS AND METHODS

A literature search of the Medline database was conducted through PubMed to identify RCT data and observational studies summarizing the risk of infection and/or malignancy in RA and specific risks associated with the use of anti-TNF-α biologic agents (adalimumab, infliximab, and etanercept). Search terms included "rheumatoid arthritis" in combination with terms relevant for each section of the article, such as "infection," "tuberculosis," "malignancy," "cancer," "lymphoma," and "TNF." Literature was selected from the last 10 years, although commonly referenced publications and highly regarded older publications were also included for consideration. RCT data were mainly limited to metaanalyses, given the limited power of data from individual RCT. Additional references were identified from the reference lists of publications in the original search and were included if relevant to the topics discussed. Narrative review articles, articles without abstracts, and case reports were excluded. Incidence and risk data for infections and malignancy were extracted and reported using the definitions from the respective publications.

RESULTS

Overview of serious infection risk in RA and with nonbiologic DMARD. Patients with RA appear to have about a 2-fold increased risk of serious infection compared to the general population and non-RA controls, irrespective of TNF-α antagonist use (Table 1)[2,3,4]. Several studies have also shown corticosteroid use is associated with increased risk of serious infection (Table 2)[2,4,5,6,7]. Smitten, *et al* noted a dose-dependent increased risk with oral corticosteroids[2]. Lacaille, *et al* observed an increased risk only in combination with DMARD (both immunosuppressive or nonimmunosuppressive agents), as corticosteroids and DMARD alone did not increase risk[5]. Brassard, *et al* suggested an increased risk for tuberculosis (TB) specifically with corticosteroids [adjusted relative risk (RR) 2.4, 95% CI 1.1–5.4] and nonbiologic DMARD (RR 3.0, 95% CI 1.6–5.8)[8].

Serious infection risk with TNF-α antagonists. Meta-analyses of RCT attempting to estimate infection risk have yielded mixed results (Table 3)[1,9,10]. In a metaanalysis of trials with monoclonal antibodies infliximab and adalimumab, Bongartz, *et al*[1] examined OR for the occurrence of ≥ 1 serious infection (anti-TNF-α vs control therapy). The pooled OR was 2.01 (95% CI 1.31–3.09) for all doses and 1.8 (95% CI 1.1–3.1) for low doses of anti-TNF-α therapy. In a separate metaanalysis that included etanercept, Alonso-Ruiz, *et al*[9] reported nonsignificant RR for all anti-TNF-α agents combined and for adalimumab, etanercept, and infliximab individually across all doses (Table 3). Risk was not assessed at recommended doses, although a significant increase was observed at high doses of infliximab ($p = 0.006$). Leombruno, *et al*[10] examined risk of infection at recommended doses and found no significant increase. An increased risk was also observed at high doses, suggesting a biological basis.

The discrepancy between data reported by Bongartz, *et al* and Leombruno, *et al* may be attributed to differences in study design. The latter analysis included etanercept studies and additional RCT data on adalimumab and infliximab (search period was through December 2007 vs December 2005)[1,10]. Given the rarity of events, these additional data likely improve the statistical power of the analysis. Additionally, Leombruno, *et al* included only published data (no abstracts) and used different classifications for the high-dose and low-dose groups for infliximab data. Nonetheless, the 3 metaanalyses collectively provide contradictory information on infection risk with anti-TNF-α therapy, although the increased risk at higher doses is consistent across studies.

Early estimates of serious infection risk associated with etanercept and infliximab by Listing, *et al* suggested a 2.7-fold to 2.8-fold increase with infliximab and etanercept, respectively, compared to DMARD controls[11]. However, after adjustment with propensity scores for age, number of DMARD failures, 28-joint count Disease Activity Score, C-reactive protein, rheumatoid factor (RF) positivity, and disability, there was no statistical difference between infliximab or etanercept and DMARD controls (Table 4)[11,12,21,22,23,26,38,39,40,41,42].

Subsequent observational studies provided more modest risk estimates, although in many cases no statistical significance was observed. For example, a study from the British Society for Rheumatology Biologics Register (BSRBR)[12] found that the adjusted incidence rate ratio (IRR) in patients that ever received anti-TNF-α therapy versus DMARD therapy was 1.35 (95% CI 0.99–1.85). When analyzed separately, no significant difference was found between DMARD and adalimumab or etanercept. However, the difference in risk was significantly greater for infliximab compared to DMARD (ever received treatment), although statistical sig-

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Table 1. Risk of infection requiring hospitalization in patients with rheumatoid arthritis (RA) compared to non-RA controls.

Study	Year	Design	Sample, n patients	Non-RA Comparator	Duration	Adjustments	Outcome	Incidence (per 100 PY) RA Cohort	Incidence (per 100 PY) Non-RA Cohort	RR (95% CI)
Doran[3]	2002	Retrospective cohort	609 RA	609 matched controls	1955-1994	Age, sex, smoking status, leukopenia, corticosteroid use, diabetes mellitus	Objectively confirmed infections	19.64	12.87	1.7 (1.4–2.0)
							Infections requiring hospitalization	9.57	5.09	1.8 (1.5–2.2)
							Any documented infection	32.05	24.04	1.5 (1.3–1.6)
Franklin[4]	2007	Prospective cohort	2108 with new onset inflammation polyarthritis	UK general population	1990-1999	Age, sex	Infections requiring hospitalization	1.21	NR*	2.7 (2.0–3.4)
							Respiratory	0.59	NR*	3.5 (2.3–5.4)
							Urinary tract	0.28	NR*	2.0 (1.2–3.4)
							Skin	0.19	NR*	1.9 (1.1–3.0)
							Septicemia	0.09	NR*	4.0 (2.0–7.8)
Smitten[2]	2008	Retrospective cohort	24,530 RA	500,000 randomly selected non-RA pts	1999–2006	Age, sex, calendar year of entry, prescription medication use at cohort entry, no. comorbid conditions prior to cohort entry	Infections requiring hospitalization	3.86	1.25	2.0 (1.9–2.1)

* Incidence rates in the RA population were compared with expected rates calculated from 10-year age, sex, and calendar year-specific hospitalization rates obtained from the regional population. PY: patient-years; NR: not reported.

Table 2. Drug-specific risks of infection requiring hospitalization with nonbiologic DMARD.

Study	Year	Design	Sample, no. patients	Comparison	Duration	Adjustments	Nonbiologic DMARD*	RR (95% CI)
Doran[6]	2002	Retrospective cohort	609 with RA	Internal controls, ever vs never	1955–1994	Age, sex, smoking status, leukopenia, corticosteroid use, diabetes mellitus	Chemotherapy	5.0 (2.4–10.3)
							Cyclophosphamide	6.1 (3.1–11.8)
							Cyclosporine	2.0 (1.3–3.2)
							Corticosteroids	1.9 (1.5–2.5)
Franklin[4]	2007	Prospective cohort	2108 with new onset inflammation polyarthritis	Internal controls, ever vs never	1990–1999	Age, sex	Steroid use	2.2 (1.5–3.4)
Bernatsky[7]	2007	Nested case-control design within an RA cohort	23,733 with RA	Internal controls, vs 10 randomly selected internal controls per reported infection	1980–2003	Other DMARD medications, no. physician visits	Azathioprine	1.5 (1.2–2.0)
							Cyclophosphamide	3.3 (2.3–4.7)
							Glucocorticoids	2.6 (2.3–2.9)
Smitten[2]	2008	Retrospective cohort	24,530 with RA	Pts with RA vs pts without RA	1999–2006	Age, sex, other current RA medications, diabetes, chronic lung disease, organic brain disease, cancer, orthopedic procedures, no. hospitalizations between cohort entry, index data and whether or not pts saw a rheumatologist during followup	Oral corticosteroids (any)	1.9 (1.7–2.2)
							≤ 5 mg/day	1.3 (1.1–1.6)
							6–10 mg/day	1.9 (1.5–2.5)
							> 10 mg/day	3.0 (2.4–3.7)
Lacaille[5]	2008	Retrospective cohort	27,710 with RA	Internal controls, vs no DMARD and no corticosteroid	1996–2003	Age, prior infection, no. prior infections, comorbidities, RA duration, and socioeconomic status	Immunosuppressant + CS	1.6 (1.5–1.8)
							Nonimmunosuppressant + CS	1.6 (1.4–1.8)
							CS alone	1.9 (0.06–2.1)

* Includes only nonbiologic DMARD shown to be associated with a significant risk of infection in the respective studies. DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; CS: corticosteroids use.

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Table 3. Pooled data from randomized controlled trials (RCT) on risk for infection and malignancy with tumor necrosis factor-α antagonists*.

Study	Year	Design	Search Period	TNF-α Antagonists Included in Analysis	Dose Groups Analyzed	Pooled OR* (95% CI)
Infection						
Bongartz[1]	2006	Metaanalysis of 9 RCT in RA	Through Dec 2005	Adalimumab, infliximab	All anti-TNF	
					All doses vs PBO	2.0 (1.3–3.1)
					Low-dose vs PBO	1.8 (1.1–3.1)
					High-dose vs PBO	2.3 (1.5–3.6)
					High-dose vs low-dose	1.4 (1.0–2.0)
Alonso-Ruiz[9]	2008	Metaanalysis of 13 RCT in RA	Up to Oct 2006	Adalimumab, etanercept, infliximab	All doses vs PBO	
					All anti-TNF	1.4 (0.8–2.2)
					Adalimumab	1.2 (0.6–2.8)
					Etanercept	0.9 (0.4–2.3)
					Infliximab	1.8 (0.9–3.4)
Leombruno[10]	2009	Metaanalysis of 18 RCT in RA	Through Dec 2007	Adalimumab, etanercept, infliximab	Recommended dose vs PBO	
					All anti-TNF	1.2 (0.9–1.6)
					Adalimumab	1.5 (0.8–2.8)
					Etanercept	0.9 (0.6–1.4)
					Infliximab	1.5 (0.9–2.5)
					High-dose vs PBO	
					All anti-TNF	2.1 (1.3–3.3)
					Adalimumab	5.8 (0.9–36.9)
					Etanercept	NA
					Infliximab	1.9 (1.2–3.0)
Malignancy						
Bongartz[1]	2006	Metaanalysis of 9 RCT in RA	Through Dec 2005	Adalimumab, infliximab	All malignancies	
					All doses vs PBO—all anti-TNF	3.3 (1.2–9.1)
					Low-dose vs PBO—all anti-TNF	1.4 (0.3–5.7)
					High-dose vs PBO—all anti-TNF	4.3 (1.6–11.8)
					High-dose vs low dose—all TNF	3.4 (1.4–8.2)
Alonso-Ruiz[9]	2008	Metaanalysis of 13 RCT in RA	Up to Oct 2006	Adalimumab, etanercept, infliximab	All malignancies	
					All doses vs PBO	
					All anti-TNF	1.5 (0.8–3.0)
					Adalimumab	1.1 (0.4–2.7)
					Etanercept	1.9 (0.6–5.7)
					Infliximab	2.6 (0.6–11.6)
Leombruno[10]	2009	Metaanalysis of 18 RCT in RA	Through Dec 2007	Adalimumab, etanercept, infliximab	Lymphoma	
					Recommended dose vs PBO	
					All anti-TNF	1.3 (0.5–3.1)
					Adalimumab	1.1 (0.3–4.1)
					Etanercept	1.4 (0.3–7.6)
					Infliximab	1.4 (0.3–7.6)
					High-dose vs PBO	
					All anti-TNF	1.1 (0.3–4.6)
					Adalimumab	1.0 (0.1–10.2)
					Etanercept	NA
					Infliximab	1.2 (0.2–7.1)
					NMSC	
					Recommended dose vs PBO	
					All anti-TNF	1.3 (0.7–2.4)
					Adalimumab	1.4 (0.5–3.9)
					Etanercept	1.0 (0.4–2.8)
					Infliximab	1.7 (0.4–7.3)
					High-dose vs PBO	
					All anti-TNF	0.9 (0.3–3.2)
					Adalimumab	0.6 (0.1–4.6)
					Etanercept	NA
					Infliximab	1.2 (0.3–5.9)

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Table 3. Continued.

Study	Year	Design	Search Period	TNF-α Antagonists Included in Analysis	Dose Groups Analyzed	Pooled OR* (95% CI)
					Noncutaneous cancers and melanomas	
					Recommended dose vs PBO	
					All anti-TNF	1.3 (0.7–2.5)
					Adalimumab	1.4 (0.5–3.9)
					Etanercept	1.1 (0.4–3.0)
					Infliximab	1.7 (0.4–7.3)
					High-dose vs PBO	
					All anti-TNF	2.9 (0.9–9.2)
					Adalimumab	2.4 (0.3–17.5)
					Etanercept	NA
					Infliximab	3.2 (0.8–12.9)
					All malignancies**	
					All anti-TNF	
					Recommended dose vs PBO	1.3 (0.8–2.4)
					High-dose vs PBO	2.5 (0.8–7.6)

* Compared to placebo arms of included RCT. ** Ad-hoc analysis of all abstracted malignancies (i.e., lymphomas, skin cancers, and noncutaneous cancers). TNF-α: tumor necrosis factor-α; RA: rheumatoid arthritis; NA: not applicable; NMSC: nonmelanoma skin cancers; PBO: placebo.

nificance depended on duration of followup. An increased risk in the first 90 days of therapy was also observed for all TNF-α antagonists individually and as a therapeutic class[12]. An updated analysis from the same registry also showed risk was highest in the first 6 months of anti-TNF-α therapy (individually and combined) compared to nonbiologic DMARD [hazard ratio (HR) 1.8, 95% CI 1.3–2.6], with no statistically significant risk observed beyond 6 months[13]. Askling, *et al* reported similar results among Swedish patients with RA receiving TNF-α antagonists[14], with the highest risk observed in the first year (RR 1.43, 95% CI 1.18–1.73) and no statistically significant risk observed during the second year (RR 1.15, 95% CI 0.88–1.51) and beyond ≥ 2 years (RR 0.82, 95% CI 0.62–1.08). A recent metaanalysis of observational studies also reported a combined RR for infection of 1.37 (95% CI 1.18–1.60), suggesting a 40% increased risk of serious infection with anti-TNF-α therapy compared to the combined comparator population across all included studies (comparators included MTX, any DMARD, and no biologic or DMARD groups)[15].

Several observational studies have also examined the risk of serious bacterial infections in patients with RA receiving a TNF-α antagonist. Curtis, *et al* analyzed administrative data in a retrospective cohort study of US patients with RA who received either anti-TNF-α therapy or MTX alone[16]. The most common bacterial infection was pneumonia and the risk of hospitalization with a physician-confirmed definite bacterial infection was about 2-fold higher overall and about 4-fold higher in the first 6 months with anti-TNF-α therapy compared to MTX alone. Dixon, *et al* also reported a similar increase in the rate of serious skin and soft-tissue infections in patients with RA receiving anti-TNF-α therapy[17]. Interestingly, Schneeweiss, *et al* found no increase in serious bacterial infections among elderly patients receiving anti-TNF-α therapy, although glucocorticoid use was associated with a dose-dependent increased risk (RR 2.1, 95% CI 1.5–3.1)[18].

TB risk with TNF-α antagonists. Of the granulomatous infections identified by Wallis, *et al* in their analysis of postmarketing surveillance data from the US Food and Drug Administration (FDA) Adverse Event Reporting System (AERS)[19,20], TB occurred with greatest frequency in both etanercept and infliximab users, with more frequent reports occurring in the infliximab group ($p < 0.0001$). Subsequent observational studies have suggested a higher incidence of TB among patients receiving monoclonal antibodies (either infliximab or adalimumab) compared to etanercept[21,22,23]. BSRBR registry data showed adjusted IRR of 3.1 (95% CI 1.0–9.5) for infliximab and 4.2 (95% CI 1.4–12.4) for adalimumab compared to etanercept[21]. These data are consistent with earlier data from the French registry (RATIO), which showed standardized incidence ratios (SIR) of 2.1 (95% CI 0.8–5.7, $p = 0.13$) for etanercept and 24.9 (95% CI 17.9–34.5, $p < 0.0001$) for adalimumab and infliximab combined in RA[22]. However, estimates of risk in the RATIO registry are based on a case-controlled analysis using crude estimates of exposure, limiting the precision of the reported risk.

Data from the Spanish biologics registry (BIOBADASER) also showed new cases of TB in patients treated with all TNF-α antagonists (i.e., adalimumab, infliximab, and etanercept), with no significant difference observed in the rate of active TB between the different antagonists[23]. However, the low statistical power of the analysis raises doubt regarding the ability to detect significant differences between groups.

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Table 4. Observational data on risk of infection and malignancy with TNF-α antagonists.

Study	Year	Registry	Period	Anti-TNF-α Agents Included in Analysis	Type of Infection	DMARD Control	Anti-TNF-α	Adalimumab	Etanercept	Infliximab
Infection										
Listing[11]	2005	RABBIT	2001–2003	Etanercept, infliximab	Serious infections					
					Rate per 100 PY (95% CI)	2.28 (1.3–3.9)	—	—	6.42 (4.5–9.1)	6.15 (4.0–9.5)
					Adjusted RR (95% CI)	Referent	—	—	2.16 (0.9–5.4)	2.13 (0.8–5.5)
Dixon[12]	2007	BSRBR	Up to July 2006	Adalimumab, etanercept, infliximab	Serious infections					
					Rate per 100 PY (95% CI)	3.92 (3.23–4.71)	6.32 (5.94–6.72)	5.42 (4.55–6.40)	6.17 (5.60–6.78)	6.89 (6.24–7.60)
					Adjusted IRR (95% CI)	Referent	1.35 (0.99–1.85)	1.25 (0.88–1.77)	1.34 (0.97–1.86)	1.41 (1.02–1.97)
Tubach[22]	2009	RATIO	2004–2007	Adalimumab, etanercept, infliximab	Tuberculosis					
					Rate per 100 PY (95% CI)	—	0.116 (0.0106–0.2229)[a]	0.215 (0.0–0.5217)[a]	0.0093 (0.0–0.0094)[a]	0.1875 (0.0001–0.03748)[a]
					SIR (95% CI)	—	12.2 (9.7–15.5)	29.3 (20.3–42.4)[a]	1.8 (0.7–4.3)[a]	18.6 (13.4–25.8)[a]
Gomez-Reino[23]	2009	BIOBAD-ASER	March 2002–Jan 2006	Adalimumab, etanercept, infliximab	Tuberculosis					
					Rate per 100 PY (95% CI)	—	—	0.176 (0.024–1.254)	0.114 (0.028–0.459)	0.383 (0.159–0.921)
Strangfeld[26]	2009	RABBIT	2001–2006	Adalimumab, etanercept, infliximab	Herpes zoster					
					Rate per 100 PY (95% CI)	0.56 (0.36–0.83)	1.01 (0.78–1.30)	1.11 (0.79–1.51)[c]	0.89 (0.56–1.33)	1.11 (0.79-1.51)[c]
					Adjusted HR (95% CI)	—	1.63 (0.97–2.74)	1.8 (1.1–3.2)[c]	1.4 (0.7–2.6)	1.8 (1.1–3.2)
					p	—	0.07	0.03	0.33	0.03
Dixon[21]	2010	BSRBR	Up to April 2008	Adalimumab, etanercept, infliximab	Tuberculosis					
					Rate per 100 PY (95% CI)	0.00 (0.00)	0.095 (0.063–0.138)	0.144 (0.072–0.258)	0.039 (0.013–0.092)	0.136 (0.068–0.244)
					Adjusted IRR (95% CI)	—	—	4.2 (1.4–12.4)	Referent	3.1 (1.0–9.5)
Malignancy										
Geborek[39]	2005	SSATG/ ARTIS	1999-2002	Etanercept, infliximab	All cancers					
					SIR (95% CI)	1.4 (1.1–1.8)	1.1 (0.6–1.8)	—	—	—
					Lymphoma (95% CI)	1.3 (0.2–4.5)	11.5 (3.7–26.9)	—	—	—
Wolfe[38]	2007	US NDB	1998–2005	Adalimumab, etanercept, infliximab	All cancers					
					OR (95% CI)	—	1.0 (0.8–1.2)	0.7 (0.3–1.6)	1.0 (0.8–1.3)	1.0 (0.8–1.3)
					p	—	0.858	0.393	0.962	0.820
					Lymphoma					
					OR (95% CI)	—	1.0 (0.5–2.0)	1.3 (0.2–10.0)	1.3 (0.6–2.8)	0.9 (0.4–2.1)
					p	—	0.967	0.826	0.460	0.898
					Melanoma					
					OR (95% CI)	—	2.3 (0.9–5.4)	0.8 (0.1–6.6)	2.4 (1.0–5.8)	2.6 (1.0–6.7)
					p	—	0.070	0.822	0.054	0.056
					NMSC					
					OR (95% CI)	—	1.5 (1.2–1.8)	0.9 (0.5–1.8)	1.2 (1.0–1.5)	1.7 (1.3–2.2)
					p	—	< 0.001	0.828	0.081	< 0.001
Askling[40]	2009	ARTIS	1999-2006	Adalimumab, etanercept, infliximab	All cancers					
					RR (Anti-TNF-α vs biologics-naive)	_	1.0 (0.9–1.2)	1.3 (0.9–2.0)	0.8 (0.6–1.0)	1.1 (0.9–1.3)
Askling[41]	2009	ARTIS	1998–2006	Adalimumab, etanercept, infliximab	Lymphoma					
					Rate per 100 PY (95% CI)	—	0.096 (0.063–0.141)	—	—	—
					RR (Anti-TNF-α vs general population)	—	2.72 (1.82–4.08)	—	—	—
					RR (Anti-TNF-α vs anti-TNF-naive)	—	1.35 (0.82–2.11)	—	—	—

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Table 4. Continued.

Study	Year	Registry	Period	Anti-TNF-α Agents Included in Analysis	Type of Infection	DMARD Control	Anti-TNF-α	Adalimumab	Etanercept	Infliximab
Mariette[42]	2010	RATIO	2004–2006	Adalimumab, etanercept, infliximab	Lymphoma					
					Rate per 100 PY (95% CI)	—	0.04 (0.007–0.08)	0.065 (0.0–0.16)	0.02 (0.0–0.05)	0.069 (0.0–0.15)
					SIR (95% CI)	—	2.4 (1.7–3.2)	4.1 (2.3–7.1)	0.9 (0.4–1.8)	3.6 (2.3–5.6)
					p	—	< 0.0001	< 0.001	0.72	< 0.001

[a] Includes data acrosss multiple indications. [b] Reported rate observed after September 2003, when all 3 agents became fully available in Spain; [c] Represents pooled results for adalimumab and infliximab. TNF-α: tumor necrosis factor-α; RABBIT: German biologics register; PY: patient-years; RR: relative risk; BSRBR: British Society for Rheumatology Biologics Register; IRR: incidence rate ratio; RATIO: French Research Axed on Tolerance of Biotherapies; SIR: standardized incidence ratio; BIOBADASER: Spanish biologics register; SSATG/ARTIS: South Swedish Anti-TNF Group Register/Swedish biologics register; US NDB: US National Data Bank for Rheumatic Diseases; HR: hazard ratio; NMSC: nonmelanotic skin cancer.

Regardless, these data show that prior to official recommendations on latent TB infection in March 2002, patients with RA who are undergoing anti-TNF-α therapy had an active TB rate 6.2-fold higher than patients with RA not treated with TNF-α antagonists[24]. Treatment of latent TB infections based on recommendations effectively and safely decreased the likelihood of active TB[24], with a 7-fold increase observed in the probability of developing TB when recommendations were not followed (incidence risk ratio 7.09, 95% CI 1.60–64.69)[23].

Other infections associated with TNF-α antagonists. An increase in the incidence of opportunistic infections, including histoplasmosis, candidiasis, listeriosis, nontuberculosis mycobacterial infections, and aspergillosis was also noted by Wallis, *et al* in their analysis of the FDA AERS postmarketing surveillance database[19,20]. Data from the CORRONA registry suggest a potential 1.7-fold increased risk (IRR 1.67, 95% CI 0.95–2.94, p = 0.077) of opportunistic infections overall with anti-TNF-α therapy compared to DMARD controls (excludes MTX and prednisone users), although statistical significance was not reached[25]. Prednisone use, smoking history, and diabetes mellitus were independent predictors of incident opportunistic infection, and prior opportunistic infection was an independent predictor of subsequent opportunistic infection. Across all treatment groups, the most frequent opportunistic infection was varicella zoster virus.

Strangfeld, *et al* have reported on the specific risk of herpes zoster, and found a statistically significant increased risk with monoclonal antibodies (combined adalimumab and infliximab) compared to DMARD[26] (HR 1.82, 95% CI 1.05–3.15). However, data did not meet the predefined outcome for clinical significance, which set a threshold HR of 2.5. No significant association was found for etanercept or pooled anti-TNF-α therapy as a class using multivariate analysis. Glucocorticoid use produced a dose-dependent increased risk independent of anti-TNF-α therapy. The risk with dosages > 10 mg/day remained significant after adjustment for age and disease severity (HR 2.52, 95% CI 1.12–5.65). No significant associations were found with MTX, leflunomide, or azathioprine. Interestingly, subgroup analysis of patients who switched between DMARD and anti-TNF-α therapy (or vice versa) showed an increased risk of herpes zoster among switchers compared to the entire cohort (adjusted HR 2.4, 95% CI 1.5–3.9)[26]. A recent report from the Spanish biologics registry (BIOBADASER) also investigated the incidence of hospitalization due to varicella zoster virus in rheumatic patients receiving TNF-α antagonists, and found a higher rate of hospitalization due to shingles and chicken pox compared to the general population [SIR 9 (95% CI 3–20) and SIR 19 (95% CI 5–57), respectively][27].

Overview of cancer risk in RA. Chronic inflammation is involved in several cancers. An estimated 18% of cancers are attributable to infection-driven inflammation[28]. Accordingly, there has been continuing debate on whether the possible increased malignancy risk seen with anti-TNF-α therapy is attributable to disease process or specific therapies. A metaanalysis of 21 observational studies showed comparable risk for all malignancies among patients with RA and the general population (SIR 1.05, 95% CI 1.01–1.09), irrespective of treatment[29]. However, risk of site-specific malignancies, including lymphoma (SIR 2.08, 95% CI 1.80–2.39) and lung cancer (SIR 1.63, 95% CI 1.43–1.87), was increased. The risk observed for Hodgkin's lymphoma (SIR 3.29, 95% CI 2.56–4.22) was greater than that for non-Hodgkin's lymphoma (NHL; SIR 1.95, 95% CI 1.70–2.24).

A metaanalysis examining the risk of lymphoma in RA confirmed a 2-fold to 3-fold increase overall, with 20 of 26 studies showing statistically significant association[30]. Prospective data from the Norfolk Arthritis Register in patients with inflammatory polyarthritis also found a 2.4-fold increased risk compared to the local population (95% CI 1.2–4.2)[31]. Subpopulations with increased risk included those with confirmed RA, those RF-positive, and

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those treated with DMARD, although patients treated with MTX were potentially at higher risk due to higher disease severity[31].

A recent population-based study across several autoimmune conditions also examined the risk of specific subtypes of NHL using the US Surveillance Epidemiology End Results-Medicare (SEER) database and found a significant association between RA and diffuse large B cell lymphoma (DLBCL; OR 1.4, 95% CI 1.2–1.5) compared to population-based controls[32]. A statistically significant increased risk of NHL, T cell NHL, marginal zone lymphoma, follicular lymphoma, and chronic lymphocytic leukemia was also reported, although in most cases the magnitude of risk was lower than that in DLBCL. These studies confirm the 2-fold to 3-fold increased risk of lymphoma and suggest that increased inflammatory activity elevates lymphoma risk. Several studies have shown an increased risk of lymphoma, and specifically DLBCL, in subpopulations with high disease activity, further supporting this hypothesis[33,34,35,36]. Lymphoma risk also appears to increase with increasing disease duration. Shared genetic susceptibility between lymphoma and RA does not appear to account for the increased risk[34,37].

Cancer risk with TNF-α antagonists. Although individual trials have reported few malignancies in patients with RA receiving anti-TNF-α therapy, the Bongartz, *et al* metaanalysis of adalimumab and infliximab RCT data raised considerable debate[1]. Pooled analysis from 9 RCT showed a significantly higher malignancy risk with anti-TNF-α monoclonal antibodies compared to placebo (Table 3). Risk was also increased at high doses of anti-TNF-α monoclonal antibodies compared to lower doses, although analysis at recommended doses was not performed. This increased risk, however, was not reproduced by Leombruno, *et al* in their metaanalysis of recommended or high doses of adalimumab, etanercept, and infliximab[10]. Specifically, no evidence of increased risk was found for lymphomas, skin cancers, and noncutaneous cancers plus melanoma with recommended or high doses of anti-TNF-α therapy compared to controls. Alonso-Ruiz, *et al* also found no increased risk of malignancy in their metaanalysis of RCT involving adalimumab, etanercept, and infliximab[9]. As discussed, inclusion of etanercept studies and additional adalimumab and infliximab studies in the Leombruno, *et al* and Alonso-Ruiz, *et al* metaanalyses may account for some of the observed differences compared to Bongartz, *et al*. In addition, aggregating malignancy data by type of cancer may reduce potential bias, given the variation in reporting practices across trials. Statistical power may also decrease given the rarity of events.

In observational studies, data from the US National Data Bank for Rheumatic Diseases suggested that users of biologics (i.e., adalimumab, anakinra, etanercept, and infliximab collectively) were not at an increased risk of cancer overall (OR 1.0, 95% CI 0.8–1.2)[38]. However, an increased risk of nonmelanotic skin cancer (OR 1.5, 95% CI 1.2–1.8) and possibly melanoma (OR 2.3, 95% CI 0.9–5.4, p = 0.070) was observed. Drug-specific risks showed infliximab and etanercept were associated with melanoma (OR 2.6, 95% CI 1.0–6.7, p = 0.056, and OR 2.4, 95% CI 1.0–5.8, p = 0.054, respectively) and nonmelanotic skin cancer (OR 1.7, 95% CI 1.3–2.2, p < 0.001, and OR 1.2, 95% CI 1.0–1.5, p = 0.081, respectively), although no association was noted for other malignancies[38].

Early reports from the Swedish Biologics Register suggested that although patients with RA receiving TNF-α antagonists were not at increased risk of overall tumors compared to the Swedish general population, there may be an increased risk for lymphoma[39]. However, other reports have shown no significant increased risk of overall cancer[40] or lymphoma[41] over the already elevated lymphoma risk in patients with RA (Table 4), despite an elevated lymphoma risk relative to the general population. The incidence and relative risk of overall cancers did not increase over time or with cumulative duration of active anti-TNF-α therapy[40]. A case-controlled study using data from the RATIO registry also showed an increased risk of lymphoma with specific TNF-α antagonists compared to the French population, although no comparison to an anti-TNF-α-naive population was performed[42]. Across all indications and for RA specifically, risk of lymphoma was higher for all TNF-α antagonists and the monoclonal antibodies compared to the general population. Treatment with adalimumab or infliximab versus etanercept was identified as a risk factor for lymphoma in the case-controlled analysis (OR 6.68, 95% CI 1.90–23.54; p = 0.003)[42].

Prior malignancy has excluded patients from participating in RCT that evaluate TNF-α antagonists. However, 2 recent observational studies have shown no significant risk of incident[43] or recurrent[44] malignancy associated with anti-TNF-α therapy in patients with RA and prior malignancy. Dixon, *et al* reported comparable rates of incident malignancy in anti-TNF-α-treated and DMARD-treated patients with RA and prior malignancy enrolled in the BSRBR registry (2.53 and 3.83 events per 100 patient-years, respectively; IRR 0.58, 95% CI 0.23–1.43)[43]. Strangfeld, *et al* also reported no significant increased risk of recurrent tumors in patients with prior malignancies compared to DMARD controls (4.55 and 3.14 events per 100 patient-years, respectively; IRR 1.4, 95% CI 0.5–5.5, p = 0.63)[44]. While these studies provide insight on risk in this subpopulation, further studies with larger datasets are required.

TNF-α antagonists and malignancy in children. Adalimumab, etanercept, and infliximab are currently approved for use in children in the United States and Canada. Concern over the possible malignancy risk in children has led to

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mandatory boxed warnings for all TNF-α antagonists. Recent analysis of postmarketing surveillance data from the FDA AERS[45] identified 48 cases of malignancy in children aged 0–18 years previously exposed to adalimumab (2 cases), etanercept (15 cases), or infliximab (31 cases) across all indications. Half of all reports were lymphomas, including hepatosplenic T cell lymphoma, NHL, and Hodgkin's disease. Reporting rates for infliximab were elevated above the general pediatric population for all malignancies (0.066 vs 0.0168 per 100 patient-years, respectively) and lymphomas (0.044 vs 0.0024 per 100 patient-years, respectively). Reporting rates for etanercept were also elevated above background for lymphomas (0.011 vs 0.0024 per 100 patient-years, respectively), although the rate for all malignancies was comparable to background (0.022 vs 0.0168 per 100 patient-years, respectively). Reporting rates were not calculated for adalimumab, as only 2 cases were identified and both reported previous use of other TNF-α antagonists.

DISCUSSION

While the FDA AERS analysis provides reason for concern, interpretation of these data requires caution. First, concomitant use of other immunosuppressants was reported in 42 of 48 patients (88%). Second, reported cases occurred across multiple indications and reporting rates do not account for background risk associated with individual diseases. Recent preliminary data from cohort studies have indicated a potential 2-fold to 3-fold increased risk for all cancers and lymphoproliferative cancers in biologic-naive patients with juvenile idiopathic arthritis (JIA) compared to the general pediatric population[46,47], suggesting risk may be overestimated when general population comparators are used. Further studies in JIA are needed to confirm these data.

The data on the rate of infection associated with TNF-α antagonists are contradictory, yet merit caution. The short duration of RCT, limited power of rare-event data, inclusion/exclusion of selected RCT, and different classification of dose groups across the metaanalyses reviewed are all potential factors that may have led to contradictory findings from RCT data. Despite the apparent contradictions, newer metaanalyses have shown a consistent increased risk of infection above recommended doses[1,10]. Complementary analyses from observational studies have provided clarity on timing of events, suggesting that the risk of infection is highest within the first year of treatment with TNF-α antagonists[12,14]. Studies have also provided a clearer understanding of the background risk of infection and malignancy in patients with RA and have suggested that the extent of risk may be lower than earlier estimates. Regarding TB and other granulomatous and intracellular infections, the risk with TNF-α antagonists is clear, thus appropriate screening is needed and continuing vigilance is important.

With respect to malignancy risk, RCT and observational data have not shown a consistent safety signal, although theoretical concerns exist. Further studies providing comparisons with anti-TNF-naive patients with RA are required to clarify the magnitude of risk above the background rate. All patients should be monitored closely for cutaneous melanomas. Malignancy risk, particularly lymphoproliferative cancers, may be increased in children and adolescents, and the data warrant caution in this population. However, further studies are required to determine background rates.

Collectively, available data on the use of TNF-α antagonists in patients with RA suggest longterm exposure is safe, although the risk of infection and malignancy remains a concern. Ongoing monitoring and increased vigilance may decrease observed risk in the long term.

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