The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: A systematic review and meta-analysis of randomized controlled trials

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Background: There is a need to better understand the safety of tumor necrosis factor (TNF) inhibitors in patients with psoriatic disease in whom TNF inhibitors are frequently used as monotherapy.

Objective: We sought to examine the risks of infection and malignancy with the use of TNF antagonists in adult patients with psoriatic disease.

Methods: We conducted a systematic search for trials of TNF antagonists for adults with plaque psoriasis and psoriatic arthritis. We included randomized, placebo-controlled trials of etanercept, infliximab, adalimumab, golimumab, and certolizumab for the treatment of plaque psoriasis and psoriatic arthritis. Twenty of 820 identified studies with a total of 6810 patients were included. Results were calculated using fixed effects models and reported as pooled odds ratios.

Results: Odds ratios for overall infection and serious infection over a mean of 17.8 weeks were 1.18 (95% confidence interval [CI] 1.05-1.33) and 0.70 (95% CI 0.40-1.21), respectively. When adjusting for patient-years, the incidence rate ratio for overall infection was 1.01 (95% CI 0.92-1.11). The odds ratio for malignancy was 1.48 (95% CI 0.71-3.09) and 1.26 (95% CI 0.39-4.15) when nonmelanoma skin cancer was excluded.

Limitations: Short duration of follow-up and rarity of malignancies and serious infections are limitations.

Conclusions: There is a small increased risk of overall infection with the short-term use of TNF antagonists for psoriasis that may be attributable to differences in follow-up time between treatment and placebo groups. There was no evidence of an increased risk of serious infection and a statistically significant increased risk in cancer was not observed with short-term use of TNF inhibitors. (J Am Acad Dermatol 2011;64:1035-50.)

Key words: biologics; cancer; infection; malignancy; meta-analysis; psoriasis; psoriatic arthritis; safety; tumor necrosis factor-alfa.

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Psoriasis is a common, chronic, inflammatory disease that is associated with impairment in health-related quality of life even when objectively mild, and an increased risk of death from cardiovascular disease, cancer, and infection in patients with severe disease.[1-7] The treatment of psoriasis has undergone a revolution with the advent of tumor necrosis factor (TNF)-alfa antagonists that suppress inflammatory pathways. These agents are generally safe and well tolerated; however, because of their immunosuppressive properties, the risk of infection and malignancy associated with these agents has been of concern.

Most studies evaluating the risks of malignancy and infection with TNF inhibitors have evaluated these agents in patients with rheumatoid arthritis (RA) or inflammatory bowel disease. Observational studies and meta-analyses of randomized controlled trials (RCTs) have indicated an increased risk of nonserious and serious infections[8-14] in these patient populations with the use of anti–TNF agents.[15-17] Some meta-analyses and observational studies in the RA population have found an increased risk of malignancy,[8,9,18,19] although there is conflicting evidence.[20-27] It is unclear, however, if safety data from patients with RA generalize to patients with psoriatic disease. In particular, patients with psoriasis are typically treated with monotherapy, whereas concomitant use of systemic immunosuppressants is common in the RA and inflammatory bowel disease patient populations.[8,9] Importantly, there may be a synergistic effect with the use of TNF antagonists and concomitant immunosuppressants on the risk of malignancy and serious infection.[28]

To date, the safety profile of these agents in patients with psoriatic disease has not been extensively evaluated. Individual RCTs lack the sample size and trial duration to detect rare adverse events such as cancer and serious infections. In addition, open-label extension trials and postmarketing surveillance databases often lack adequate control groups and spontaneous reports are generally not reliable for assessing malignancy and infection risk as a result of severe underreporting.[29] In this study, we sought to evaluate the risk of malignancy, serious infection, and nonserious infection associated with the use of anti–TNF-alfa agents in adult patients with plaque psoriasis (PsO) and psoriatic arthritis (PsA) by conducting a meta-analysis of RCTs.

CAPSULE SUMMARY

- We examined the risks of infection and malignancy with the use of tumor necrosis factor-alfa antagonists in adult patients with psoriatic disease through a meta-analysis of randomized controlled trials.
- Twenty trials of etanercept, infliximab, adalimumab, golimumab, and certolizumab involving 6810 patients were included.
- In contrast to previous meta-analyses of tumor necrosis factor inhibitors for rheumatoid arthritis, we found no increased risk of overall infection when adjusting for follow-up time, and no evidence of a statistically significant increased risk of serious infection or cancer with the short-term use of these agents.
- Larger, long-term studies are necessary to assess the risks associated with chronic use of tumor necrosis factor inhibitors in the psoriatic population.

METHODS

Based on the *Cochrane Handbook for Systemic Reviews of Interventions* guidelines,[30] we used a predefined, peer-reviewed protocol to perform the study selection, assessment of eligibility criteria, data extraction, and statistical analysis of RCTs of patients with PsO and PsA. This article was prepared in accordance with the PRISMA statement.[31] This study was granted an institutional review board exemption by the University of Pennsylvania.

Data sources and search strategy

We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from inception to July 30, 2009, using the terms "psoriasis" and "psoriatic arthritis" combined with "controlled trial," "clinical trial phase II," "clinical trial phase III," "clinical trial phase IV," and "randomized trial," combined with "biological," "biologics," "TNF," "tumor necrosis factor," or with terms specific to each biologic agent including "etanercept," "Enbrel," "infliximab," "Remicade," "adalimumab," "Humira," "golimumab," "CNT0 148," "certolizumab," and "CDP870." To obtain data from unpublished or unidentified clinical studies, we searched clinicalstudyresults.org and contacted industry sponsors of the anti–TNF agents and corresponding authors of published studies (Centocor, Horsham, PA; Schering-Plough, Kenilworth, NJ; Abbott Laboratories, Abbott Park, IL; Amgen, Thousand Oaks, CA; and UCB Inc, Smyrna, GA).

Selection and outcomes

We included RCTs of the 4 currently licensed anti–TNF agents (etanercept, infliximab,

Abbreviations used:

CI:	confidence interval
DMARD:	disease-modifying antirheumatic drug
IRR:	incidence rate ratio
NMSC:	nonmelanoma skin cancer
OR:	odds ratio
PsA:	psoriatic arthritis
PsO:	plaque psoriasis
PY:	patient-year
RA:	rheumatoid arthritis
RCT:	randomized controlled trial
SAE:	serious adverse event
TNF:	tumor necrosis factor

adalimumab, golimumab), and one anti−TNF agent currently under investigation (certolizumab) for the treatment of adult patients with moderate to severe PsO, PsA, or both, limited to the English language. Study participants must have been adult patients with a diagnosis of PsO or PsA randomized to receive treatment with an anti−TNF agent or placebo for at least 12 weeks.

Studies were evaluated by two independent reviewers (K. A. and J. N.) using the scale of Jadad et al,[32] which scores the quality of studies on a scale of 0 to 5. A Jadad score of 3 or greater was required for inclusion; this primarily indicates blinding, randomization, and report of withdrawals and dropouts.

Data abstraction

Data were independently abstracted by two authors (K. A. and E. D. D.) for our two primary outcomes of malignancy and infection, with disagreement resolved by consensus. We also classified infections as serious or nonserious. Serious infection was defined as an infection that was considered a serious adverse event (SAE), and nonserious infection as an infection that was not recorded as an SAE by study investigators. We classified reported malignancies as nonmelanoma skin cancers (NMSC) and a composite group of other cancers. We obtained the time point of diagnosis for each malignancy and person-years of follow-up for each treatment arm from published reports, industry sponsors, or both. All industry sponsors and corresponding authors were contacted to verify and/or obtain (if not reported in the original publication) the number of infections and malignancies. We were able to obtain requested unpublished data from all of the above sponsors except UCB Inc.

Data on the following measures were also abstracted: study design, sample size, intention-to-treat analysis, trial duration, blinding period, outcome measures, treatment regimen, and withdrawals and dropouts.

Statistical analysis

We determined the number of patients with at least one infection or malignancy during the randomized, placebo-controlled period. In instances where the number of events instead of the number of subjects experiencing an event was reported, an assumption of one event per subject was made. All patients from eligible trials who received at least one dose of study drug were included in the denominator of our outcome measures (intention-to-treat method). We calculated an odds ratio (OR) based on the number of subjects experiencing the events (malignancy, infection) and the number of subjects receiving treatment in each group. Homogeneity testing was performed using the I^2 test.[33] We produced a pooled estimate of risk for each outcome, with results expressed as overall ORs with associated 95% confidence intervals (CIs). A fixed effects model with Mantel-Haenszel methods[34] was used, as it is considered to be superior to a random effects model when pooling trials with few or no events and typically produces narrower CIs.[30] We calculated ORs across all included studies, and performed subanalyses by indication and drug. We calculated a number needed to harm based on the Mantel-Haenszel fixed effects model estimate if the OR was statistically significant.

We also calculated rate-adjusted estimates of risks for malignancy and infection using incidence rate ratios (IRRs). The rate ratio was calculated for each study based on the number of events and person-years of follow-up in each treatment group. The IRR was calculated by pooling the rate ratios across studies using Mantel-Haenszel weights.[35]

All treatment regimens (eg, low dose, high dose) were combined for comparison. We observed zero events in some groups for some of the outcome measures, particularly malignancy. For both the OR and IRR calculations, when no events were observed in one arm of the RCT, we used a continuity correction of 0.5.[36] If no events occurred in either study arm, the study was effectively excluded from the analysis.

Sensitivity analyses included calculating ORs of the pooled estimates of risk using the random effects model, and calculating the ORs and IRRs using multiple different continuity corrections. We also performed an analysis omitting all NMSC. The influence of individual studies on the pooled effect size estimate was analyzed by performing an influence analysis, in which the pooled estimates were recalculated omitting one study at a time. We used funnel plots to evaluate the potential for publication bias with respect to our primary end points (malignancy and infection).[30,37-39] We also used the Egger test to evaluate the risk of publication bias, with a 2-tailed

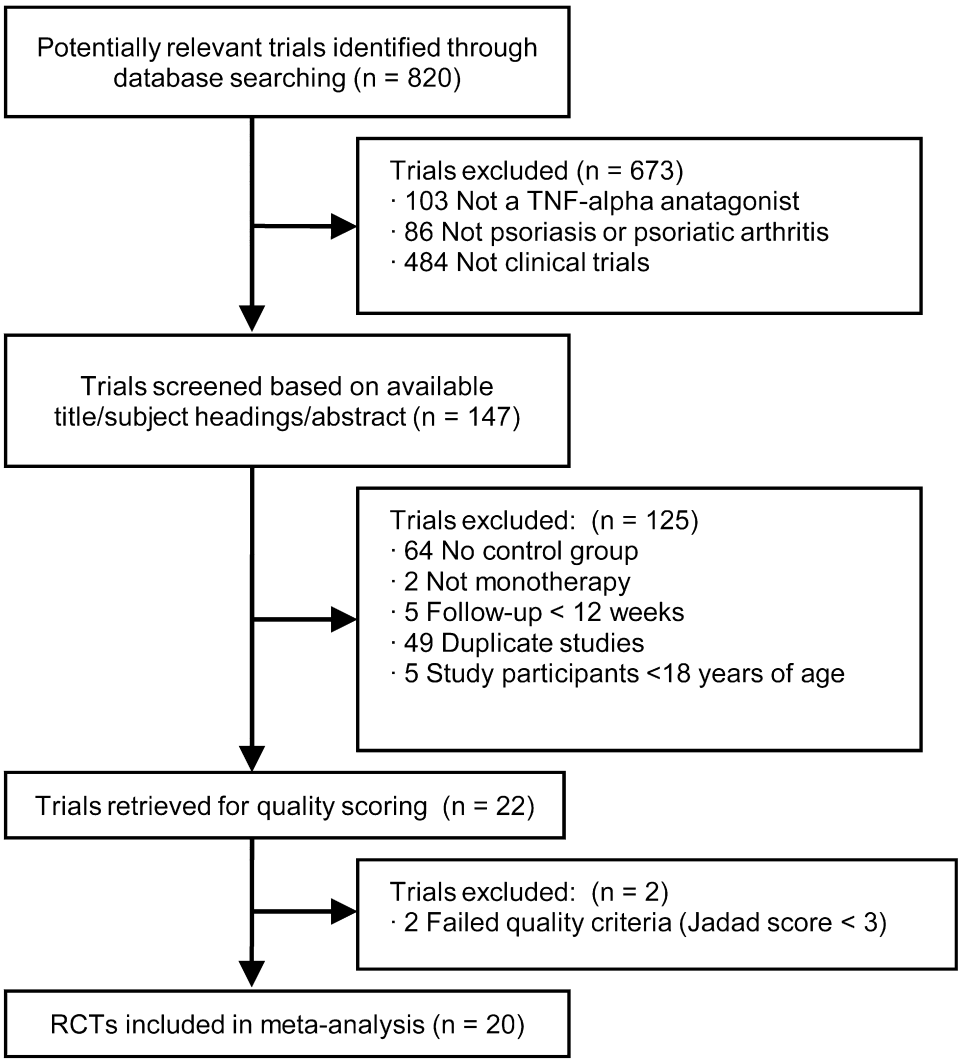

Fig 1. Selection of studies for meta-analysis. *RCT*, Randomized controlled trial; *TNF*, tumor necrosis factor.

P value of less than .05 considered to be statistically significant.[30]

All analyses were performed using Stata (Version 10.0, StataCorp, College Station, TX) and Review Manager (Version 5.0.21, Nordic Cochrane Center, Copenhagen, Denmark).

RESULTS

Search results and trial characteristics

Of 820 potentially relevant publications identified through database searching, 20 clinical trials including 6810 adult patients (5427 patients in PsO and 1383 patients in PsA studies) qualified for inclusion (Fig 1). Seven trials specifically included patients with active PsA unresponsive to disease-modifying antirheumatic drugs (DMARD), nonsteroidal anti-inflammatory drugs, or both, although 5 of these trials also required that patients have active psoriatic skin lesions, a documented history of PsO, or both. The remaining 13 trials specifically included those with moderate to severe PsO. All PsA trials allowed for the use of at least one concomitant DMARD, whereas PsO trials excluded those on concomitant immunosuppressant therapy.

All trials compared one of the following treatments with a placebo: 6 trials with adalimumab, 7 with etanercept, 5 with infliximab, 1 with certolizumab, and 1 with golimumab. Two separate 24-week trials were designed with early escape at week 16, which allowed patients to enter either the treatment group from placebo or begin a higher dose of study drug if there were two treatment groups in the trial. For these trials, any patient who received at least one dose of anti—TNF treatment was included in the treatment group.[40] This resulted in 4598 patients included in the treatment group and 2313 patients

Table I. Trial characteristics

Source	Trial name/registry No.	Disease indication	Permitted concomitant systemic therapy	Duration of placebo-controlled trial, wk	Treatment group (n = 4598)			Placebo group (n = 2313)	
					Treatment (dose)	No. of patients	Patient-years follow-up	No. of patients	Patient-years follow-up
Mease et al,[47] 2005	Study M02-518 / NCT00646386	PsA	MTX (≤30 mg/wk) or prednisone (≤10 mg/d) at stable dose; rescue therapy after wk 12 with DMARD or corticosteroids	24	Adalimumab (40 mg eow)	151	66.8	162	71.1
Gordon et al,[46] 2006	Study M02-528 / NCT00645814	PsO	None	12	Adalimumab (40 mg eow)	45	10.2	52	11.8
					Adalimumab (40 mg weekly)	50	11.2		
Genovese et al,[57] 2007	Study M02-570 / NCT00646178	PsA	MTX (≤30 mg/wk) or prednisone (≤10 mg/d), or other DMARD at stable dose	12	Adalimumab (40 mg eow)	51	11.8	49	10.8
Menter et al,[50] 2008	Study M03-656 / NCT00237887	PsO	None	16	Adalimumab (80 mg at wk 0, then 40 mg eow starting at wk 1)	814	250.4	398	120.7
Saurat et al,[51] 2008	CHAMPION/study M04-716 / NCT00235820	PsO	None	16	Adalimumab (80 mg at wk 0, then 40 mg eow starting at wk 1)	108	34.7	52	16.3
					MTX (7.5 mg, increased as needed and as tolerated to 25 mg weekly)*	110	34.8		
Akihiko et al,[78] 2010	Study M04-688 / NCT00338754	PsO	None	24	Adalimumab (80 mg at wk 0, then 40 mg eow starting at wk 1)	38	16.3	46	19.1
					Adalimumab (40 mg eow)	43	17.2		
					Adalimumab (80 mg eow)	42	17.9		
Unpublished[41]	Study C87040 / NCT00245765	PsO	None	12	Certolizumab pegol (400 mg at wk 0, then 200 mg every 2 wk)	59	Unknown	59	Unknown
					Certolizumab pegol (400 mg every 2 wk)	58			

Continued

Table I. Cont'd

Source	Trial name/registry No.	Disease indication	Permitted concomitant systemic therapy	Duration of placebo-controlled trial, wk	Treatment group (n = 4598)			Placebo group (n = 2313)	
					Treatment (dose)	No. of patients	Patient-years follow-up	No. of patients	Patient-years follow-up
Mease et al,[48] 2000	Study 20021630	PsA and PsO	MTX (≤25 mg/wk) or prednisone (≤10 mg/d) at stable dose	12	Etanercept (25 mg twice weekly)	30	6.5	30	6.1
Gottlieb et al,[52] 2003	Study 20021632	PsO	None	24	Etanercept (25 mg twice weekly)	57	23.6	55	14.5
Leonardi et al,[42] 2003	Study 20021639	PsO	None	12	Etanercept (25 mg weekly)	160	34.3	166	34.9
					Etanercept (25 mg twice weekly)	162	34.6		
					Etanercept (50 mg twice weekly)	164	35.8		
Mease et al,[49] 2004	NCT00317499	PsA	MTX (≤25 mg/wk) or prednisone (≤10 mg/d) at stable dose	24	Etanercept (25 mg twice weekly)	101	81.0	104	59.2
Papp et al,[44] 2005	Study 20021642	PsO	None	12	Etanercept (25 mg twice weekly)	196	42.9	193	41.0
					Etanercept (50 mg twice weekly)	194	42.6		
Tyring et al, 2006[55]	NCT00111449	PsO	None	12	Etanercept (50 mg twice weekly)	312	68.8	306	65.9
van de Kerkhof et al,[43] 2008	NCT00333034	PsO	None	12	Etanercept (50 mg weekly)	96	Unknown	46	Unknown
Kavanaugh et al,[45] 2009	NCT00265096	PsA	Stable dose of MTX, prednisone, or NSAID	24 with early escape at wk 16	Golimumab (50 mg every 4 wk)	146	62	113	42
					Golimumab (100 mg every 4 wk)	146	67		
					All golimumab†	343	142		
Gottlieb et al,[58] 2004	SPIRIT / NCT00230529	PsO	NSAID	30	Infliximab (3 mg/kg at wk 0, 2, 6)	98	56	51	20.5
					Infliximab (5 mg/kg at wk 0, 2, 6)	99	58		
Antoni et al,[56] 2005	IMPACT	PsA	MTX or other DMARD at stable dose	16	Infliximab (5 mg/kg at wk 0, 2, 6, 14)	52	16	51	16
Antoni et al,[40] 2005	IMPACT 2 / NCT00051623	PsA	MTX (≤25 mg/wk) or prednisone (≤10 mg/d) at stable dose	24 with early escape at wk 16	Infliximab (5 mg/kg at wk 0, 2, 6, 14, 22)	100	45	97	37
					All infliximab†	150	53		

Reich et al,[54] 2005	EXPRESS I / NCT00106834	PsO	NSAID	24	Infliximab (5 mg/kg at wk 0, 2, 6, 14, 22)	298	135	76	33
Menter et al,[53] 2007	EXPRESS II / NCT00106847	PsO	NSAID	14	Infliximab (3 mg/kg at wk 0, 2, 6)	313	85	207	54
					Infliximab (5 mg/kg at wk 0, 2, 6)	314	85		

DMARD, Disease-modifying antirheumatic drugs; *eow*, every other week; *MTX*, methotrexate; *NSAID*, nonsteroidal anti-inflammatory drugs; *PsA*, psoriatic arthritis; *PsO*, plaque psoriasis.
*Not included in meta-analysis.
†Includes all patients who received at least one dose of study drug.

included in the placebo group for the meta-analysis (see Table I for trial characteristics).

One clinical trial was not published in a peer-reviewed journal, and data on this study were obtained through a poster abstract.[41] We found no trials meeting our inclusion-criteria that were published in a language other than English. Mean duration of the placebo-controlled phases across trials was 17.8 weeks (range 12-30 weeks). Overall, the percent of withdrawals during the course of the study was significantly greater in the placebo group than in the treatment group (16.1% vs 6.8%, $P = .005$). According to the published manuscripts, the greater withdrawal rate in the placebo group was largely a result of lack of efficacy. One study did not report dropouts specifically for each treatment group, but did report overall dropouts and an adequate description of appropriate double blinding, and thus qualified for inclusion according to the criteria of Jadad et al.[32,42] Similarly, there was a significant difference in patient-years (PY) of follow-up between treatment and placebo groups (total of 1516.4 and 673.9 PY, respectively, $P = .0004$), partially because of differential dropout between the placebo and treatment groups, but also because many trials included multiple treatment groups for different doses of study drug (Table I). We were unable to obtain information on PY of follow-up for two studies.[41,43]

Malignancies

A total of 21 malignancies were reported in published data in patients who received at least one dose of an anti−TNF agent and 4 malignancies in patients who received placebo across the 20 included clinical trials. An additional 7 malignancies (4 basal cell carcinomas, one squamous cell carcinoma, one prostate cancer, and one breast cancer) in the treatment group and two malignancies (two squamous cell carcinomas) in the placebo group were identified after contacting the industry sponsors.[42,44] A total of 28 malignancies in the treatment group and 6 malignancies in the placebo group were used in the analysis (Table II).

The pooled OR for malignancies in patients with PsO and PsA using anti−TNF agents was 1.48 (95% CI 0.71-3.09). We found no evidence of statistical heterogeneity, the measure of inconsistency between trials ($I^2 = 0.0\%$, $P = .91$). We also conducted subanalyses by drug (Fig 2). Using the rate-adjusted analysis, we found an IRR of 0.99 (95% CI 0.51-1.90).

Two 24-week trials were designed with early escape at week 16. In the study by Kavanaugh et al,[45] all malignancies occurred in patients receiving only the 100-mg dose of golimumab throughout

Table II. Malignancies and infectious events occurring in randomized controlled trials

		Treatment group (n = 4598)						Placebo group (n = 2313)					
Source	Treatment (dose)	No. of patients	Patients with ≥1 serious infection	Patients with ≥1 infectious event	No. of malignancies	Type of malignancy	Time of malignancy, wk	No. of patients	Patients with ≥1 serious infection	Patients with ≥1 infectious event	No. of malignancies	Type of malignancy	Time of malignancy, wk
Mease et al,[47] 2005	Adalimumab (40 mg eow)	151	1	68	0			162	1	64	0		
Gordon et al,[46] 2006	Adalimumab (40 mg eow)	45	0	5	1	Metastatic SCC*	2.1	52	0	8	0		
	Adalimumab (40 mg weekly)	50	1	13	1	Breast cancer	5.1						
Genovese et al,[57] 2007	Adalimumab (40 mg eow)	51	0	9	0			49	1	16	0		
Menter et al,[50] 2008	Adalimumab (80 mg at wk 0, then 40 mg eow starting at wk 1)	814	5	235	6	NMSC × 4 Breast cancer Melanoma in situ	8.1, 8.1, 13, 15.6 1.6 4.1	398	4	89	2	NMSC Uterine carcinoma	13.9 4.1
Saurat et al,[51] 2008	Adalimumab (80 mg at wk 0, then 40 mg eow starting at wk 1)	108	0	51	0			52	0	23	0		
Akihiko et al,[78] 2010	Adalimumab (80 mg at wk 0, then 40 mg eow starting at wk 1)	38	0	21	0			46	0	23	0		
	Adalimumab (40 mg eow)	43	0	18									
	Adalimumab (80 mg eow)	42	0	21									
Unpublished[41]	Certolizumab pegol (400 mg at wk 0, then 200 mg every 2 wk)	59	1	16	0			59	0	24	0		
	Certolizumab pegol (400 mg every 2 wk)	58	2	27									
Mease et al,[48] 2000	Etanercept (25 mg twice weekly)	30	0	17†	0			30	0	17†	0		
Gottlieb et al,[52] 2003	Etanercept (25 mg twice weekly)	57	0	28‡	0			55	1	14‡	0		

Leonardi et al,[42] 2003	Etanercept (25 mg weekly)	160	2	18‡	1§	BCC§	11.6	166	2	22‡	2§	SCC × 2§	0.7, 1.9
	Etanercept (25 mg twice weekly)	162	0	15	0								
	Etanercept (50 mg twice weekly)	164	1	10	2§	BCC§ Prostate cancer§	9.1 7.3						
Mease et al,[49] 2004	Etanercept (25 mg twice weekly)	101	0	33	0			104	1	39	0		
Papp et al,[44] 2005	Etanercept (25 mg twice weekly)	196	1	36//	0			193	1	29//	0		
	Etanercept (50 mg twice weekly)	194	0	35	4§	Breast cancer§ SCC§ BCC × 2§	1.9 7.9 8.0, 12.0						
Tyring et al, 2006[55]	Etanercept (50 mg twice weekly)	312	1	88	3	SCC BCC Pancreatic carcinoma	0.6 Unknown 10.7	306	1	71	1	Bladder carcinoma	11.0
van de Kerkhof et al,[43] 2008	Etanercept (50 mg weekly)	96	0	27	0			46	0	12	0		
Kavanaugh et al,[45] 2009	Golimumab (50 mg every 4 wk)	146	1	48	0	BCC × 2	19.3, 19.8	113	4	27	0		
	Golimumab (100 mg every 4 wk)	146	1	60	3	Prostate cancer	9.9						
	All golimumab¶	343	2	118	3	*As above*	*As above*						
Gottlieb et al,[58] 2004	Infliximab (3 mg/kg at wk 0, 2, 6)	98	0	31	2	SCC × 2	8.9, 7.8	51	0	11	0		
	Infliximab (5 mg/kg at wk 0, 2, 6)	99	1	37	1	BCC	31.8						
Antoni et al,[56] 2005	Infliximab (5 mg/kg at wk 0, 2, 6, 14)	52	1	6	0			51	0	9	0		
Antoni et al,[40] 2005	Infliximab (5 mg/kg wk 0, 2, 6, 14, 22)	100	3	34	0			97	2	29	1	BCC	9.9
	All infliximab#	150	3	47	0								
Reich et al,[54] 2005	Infliximab (5 mg/kg wk 0, 2, 6, 14, 22)	298	3	125	2	SCC BCC	5.7 5.2	76	0	30	0		

Continued

Table II. Cont'd

Source	Treatment (dose)	Treatment group (n = 4598)						Placebo group (n = 2313)					
		No. of patients	Patients with ≥1 serious infection	Patients with ≥1 infectious event	No. of malignancies	Type of malignancy	Time of malignancy, wk	No. of patients	Patients with ≥1 serious infection	Patients with ≥1 infectious event	No. of malignancies	Type of malignancy	Time of malignancy, wk
Menter et al,[53] 2007	Infliximab (3 mg/kg at wk 0, 2, 6)	313	0	106	1	BCC	9.9	207	1	62	0		
	Infliximab (5 mg/kg at wk 0, 2, 6)	314	1	97	1	BCC	9.4						

BCC, Basal cell carcinoma; *eow,* every other week; *NMSC,* nonmelanoma skin cancer (unspecified); *SCC,* squamous cell carcinoma.
*Noncutaneous metastatic SCC on left side of neck. Swollen lymph node on left side of neck was present at screening.
†Only upper respiratory tract events reported.
‡Only upper respiratory tract infections and sinusitis reported.
§A total of 9 malignancies were unpublished and obtained from industry sponsors.
//Only upper respiratory tract infections and flu syndrome reported.
¶All golimumab group includes all patients who received at least one dose of study drug. All malignancies occurred in patients receiving only 100-mg dose.
#Includes all patients who received at least one dose of study drug.

the 24 weeks. In another trial by Antoni et al,[40] of infliximab, only one malignancy occurred in the trial in a patient receiving placebo.

Overall, 70.6% of malignancies included in our analysis were NMSC. The OR for NMSC in patients using anti—TNF agents across all trials was 1.33 (95% CI 0.58-3.04). The IRR for NMSC was 0.72 (95% CI 0.42-1.24).

The OR for all malignancies excluding NMSC was 1.28 (95% CI 0.39-4.15). Subanalysis by disease indication resulted in an OR of 0.83 (95% CI 0.14-4.96) for PsA trials (n = 7) and an OR of 1.64 (95% CI 0.73-3.70) for PsO trials (n = 13). Similar results were obtained when using a Mantel-Haenszel random effects model, with ORs of 1.38 (95% CI 0.64-3.01) and 1.23 (95% CI 0.37-4.06) for all malignancies and malignancies excluding NMSC, respectively. The rate-adjusted analysis for all malignancies excluding NMSC yielded an IRR of 0.56 (95% CI 0.31-1.01).

Infections

A total of 1358 patients in the treatment group and 619 patients in the placebo group experienced an infectious event (serious or nonserious). Several studies (n = 7)[43,46-51] did not specify whether reported nonserious infections were by number of events or by number of patients experiencing at least one nonserious infection. For nonserious infections, 4 studies[42,44,48,52] only reported patients experiencing the most common infections that occurred during the trial, which included upper respiratory tract infections, flu syndrome, and sinusitis (Table II).

The OR for any infectious event in patients with PsA or PsO treated with an anti—TNF agent was 1.18 (95% CI 1.05-1.33), with 97.6% of infections being nonserious, ie, not recorded as an SAE. The ORs were 1.22 (95% CI 1.06-1.40) for PsO trials and 1.09 (95% CI 0.87-1.37) for PsA trials when separating by indication. We also stratified the risk of infection by drug (Fig 3). The number needed to harm for treatment with all anti—TNF agents was 29. There was no evidence of statistically significant heterogeneity (I^2 = 21.6%, P = .187). The estimated OR for nonserious infection only was 1.20 (95% CI 1.07-1.35).

Serious infections were reported in 28 (0.61%) patients in the treatment group and 19 (0.82%) patients in the placebo group, resulting in a pooled OR of 0.70 (95% CI 0.40-1.21). Stratification by disease indication resulted in an OR of 0.78 (95% CI 0.38-1.58) for PsO and 0.60 (95% CI 0.25-1.44) for PsA. Similar results were found when using a random effects model.

When adjusting for PY, the IRR for overall infection was 1.01 (95% CI 0.92-1.11) and 0.59 (95% CI

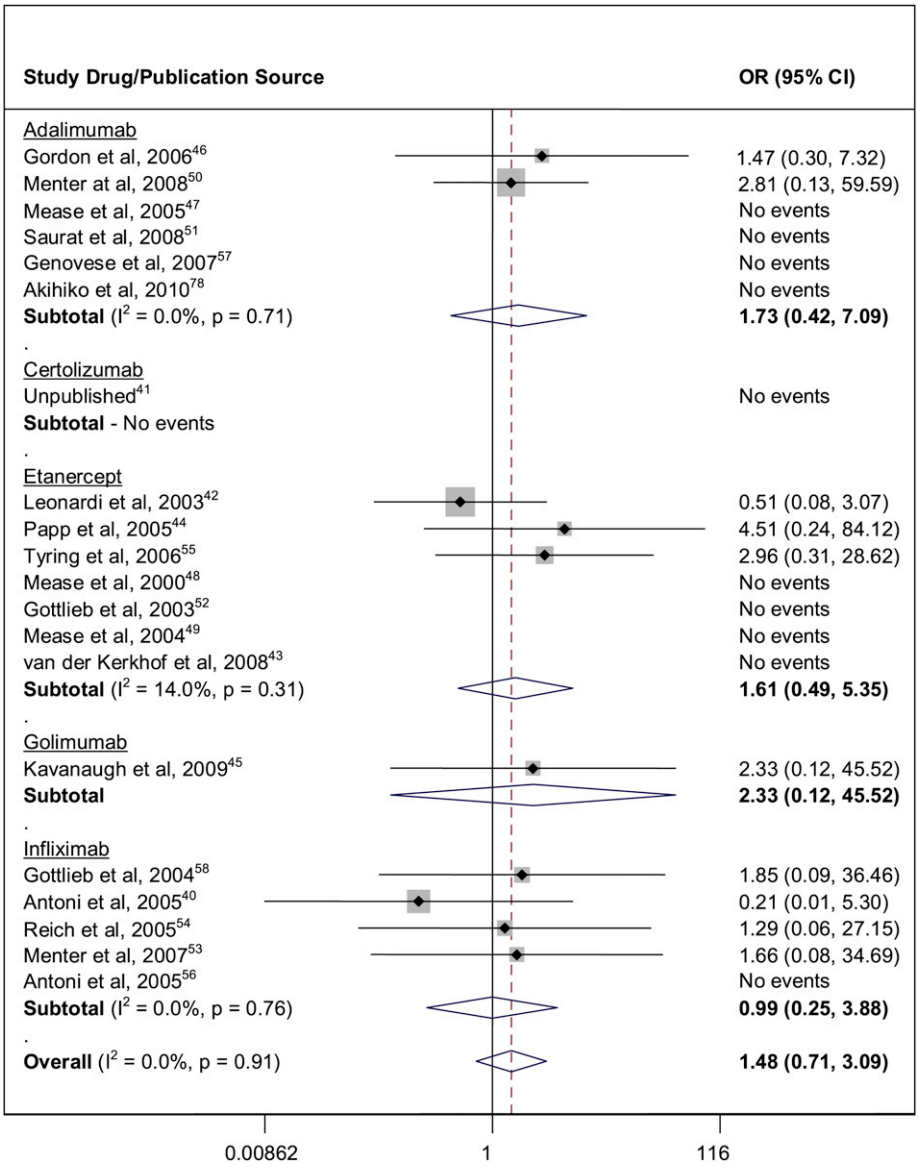

Fig 2. Odds ratio (*OR*) of malignancy associated with anti–tumor necrosis factor (*TNF*) treatment versus control. *CI*, Confidence interval. For each study, central diamond indicates mean effect, line represents 95% CI, and size of grey square represents the study's weight in the pooling. Large diamonds represent combined ORs and 95% CIs of studies in each subgroup (by drug) and overall. Dashed red line indicates the pooled OR across all studies.

0.35-0.99) for serious infection. The estimated IRR for nonserious infection was 1.02 (95% CI 0.93-1.13).

Publication bias

We found no evidence of publication bias with Egger tests for malignancy ($P = .54$), NMSC ($P = .29$), malignancies excluding NMSC ($P = .48$), overall infection ($P = .18$), nonserious infection ($P = .16$), or serious infection ($P = .14$). Funnel plots were also created for the above outcomes, all of which were found to be symmetric.

DISCUSSION

Our systematic review and meta-analysis combined data from 20 RCTs of adult patients with PsO and PsA treated with anti–TNF-alfa agents. To our knowledge, this is the largest review to date of RCTs examining the risk of infection and malignancy with the use of anti–TNF-alfa agents in patients with psoriatic disease.

Our study suggests that there may be a small increased risk of overall infection with the short-term use of TNF-alfa antagonists for psoriatic disease.

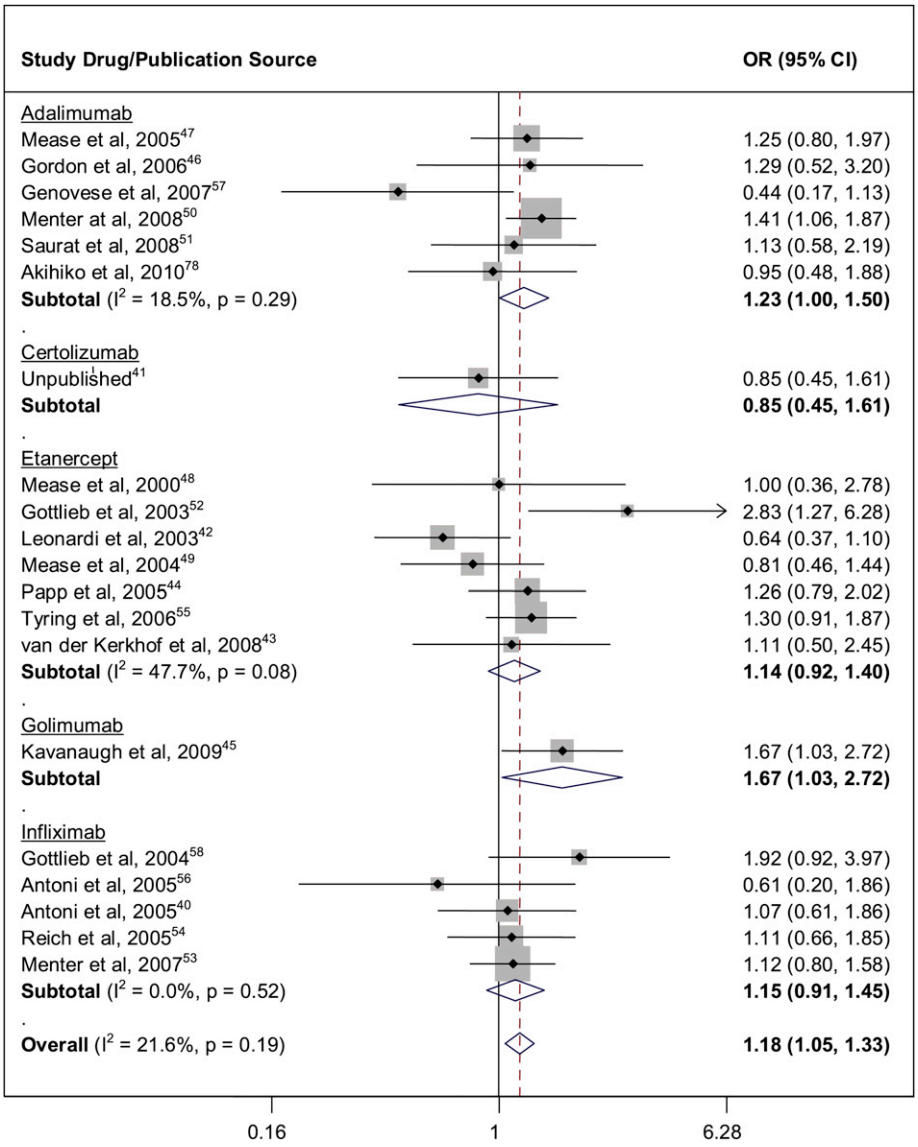

Fig 3. Odds ratio (*OR*) of overall infection associated with anti–tumor necrosis factor (*TNF*) treatment versus control. *CI*, Confidence interval.

However, 97.6% of reported infections were nonserious, and the large majority of these were upper respiratory tract infections. Thus, although our finding for an increased risk of overall infection may be statistically significant, it may have limited clinical implications, and it appears that the short-term risk-to-benefit profile with respect to overall infection is favorable. Moreover, models that adjust for differences in follow-up time indicated no statistically significant increased risk of infection, suggesting that the observed infection risk may be an effect of differential follow-up as opposed to an effect of the TNF inhibitor.

There was no evidence of an increased risk of serious infection and a statistically significant increased risk of cancer was not observed. When adjusting for PY of follow-up, we found a marginally statistically significant decreased risk of serious infection.[41,42,44,50,53-55] From the 9 trials with detailed information,[40,45-47,49,52,56-58] cellulitis was the most common serious infection occurring in the placebo group (n = 3) compared with only one reported case in the treatment group. Thus, an improvement in skin disease and decreased scratching with anti–TNF therapy may be a plausible explanation for this unexpected finding. It must be emphasized, however, that serious infections including atypical infections such as tuberculosis have been reported in a variety of TNF inhibitor–treated patient populations including patients with psoriatic disease. Therefore, clinicians should ensure that patients are up to date with vaccinations, and have appropriate screening for

tuberculosis and invasive fungal infections before initiation of TNF inhibitors, and are closely monitored for infection during the course of treatment.[59]

Our study results differ from a similar meta-analysis performed in the RA population by Bongartz et al[8] that found pooled ORs of 3.3 (95% CI 1.2-9.1) for malignancy and 2.0 (95% CI 1.3-3.1) for serious infection with the use of anti—TNF antibodies (infliximab and adalimumab). This meta-analysis included 9 RCTs, limited to the placebo-controlled phase. Despite our inclusion of a greater number of trials with more patients, more malignancies and serious infections occurred in the meta-analysis by Bongartz et al then in our analysis of patients with psoriatic disease. This difference in safety profile is consistent with results from open-label studies of etanercept in psoriasis and RA, which found the exposure-adjusted rates of serious infectious events in the psoriasis population to be lower than that in the RA population (1.2 vs 4.2 events/100 PY, respectively).[60,61]

Several factors could explain the differing results between our meta-analysis and that of the meta-analysis in the RA population. On average, the duration of the placebo-controlled phases of the included trials for the analysis of Bongartz et al[8] was longer than those included in our study (mean of 32.7, range 12-54 weeks compared with mean of 17.8, range 12-30 weeks for our study), which could have led to increased detection of adverse events, especially if the risk increases over time. However, others have found in the RA population that serious infections appear to peak in the first 90 days of treatment with an anti—TNF agent.[62] In addition, the large majority of malignancies reported in the study by Bongartz et al[8] occurred within the first 24 weeks (24 vs 8 occurring at >24 weeks in the randomized-controlled phases of the trials).

The most notable difference between the trials included in our meta-analysis and previous meta-analyses done within the RA population was the use of concomitant immunosuppressive therapy. In the trials included in the meta-analysis by Bongartz et al[8] (n = 5005), approximately 77.1% of the patients were on methotrexate, 6.5% were on other DMARD, and 54.9% were on corticosteroids concomitantly at baseline.[63-71] In the 13 PsO trials (n = 5434) included in our meta-analysis, none allowed for simultaneous immunosuppressive therapy, and in the 7 included PsA trials (n = 1485), approximately 44.6% were on methotrexate, 5.5% were on other DMARD, and 10.5% were on corticosteroids at baseline. There is some evidence that there may be a synergistic effect when combining other systemic immunosuppressants with TNF-alfa inhibitors on the risk of serious infection and malignancy.[72-76] This suggests that the risk profile of these agents may be significantly altered when using combination therapy, and that this should be taken into account when interpreting the existing literature.

Limitations

There are several limitations to our study that should be noted. Conducting meta-analyses with rare event data is inherently difficult. Small changes in the numerator or denominator can significantly affect the estimated risk. Because of the rarity of events and short duration of follow-up, the CIs we calculated for malignancy and serious infection were wide and do not rule out potential associations that could be clinically significant. Moreover, safety end points were grouped (eg, serious infections, malignancy) and, therefore, this analysis could not determine the risk of specific individual outcomes such as tuberculosis or lymphoma. In addition, we were unable to assess the risk of cancer and serious infection associated with chronic use of TNF inhibitors. This limitation is of special concern for malignancy, which may take years of exposure to accurately define risk. In general, side effects that are delayed in onset or occur at a rate of less than 1 in 1000 patients per year are often only recognized after a medication is in widespread use, with more than half of medications entering the market having SAEs discovered only after Food and Drug Administration approval. Thus, it has been suggested that a novel drug should have at least 20,000 patients exposed with direct observation (ie, active surveillance for adverse events as opposed to relying on spontaneous reports) before being widely marketed to the general population.[77]

On average, the clinical trials included in our meta-analysis often had shorter durations of follow-up in placebo groups compared with treatment groups because of higher rate of treatment failure in the former. Because our pooled ORs were based on event data, longer follow-up time in the treatment groups could have biased our results to an overestimation of the true risk, as there is more time in the treatment group to detect an adverse event. To adjust for unequal follow-up times, we performed a meta-analysis of rates. However, the statistical methods are not as well developed for this type of analysis, and it requires an assumption of a constant, underlying risk, which may not be appropriate.[30] Thus, although the rate-adjusted estimates are informative, they should be interpreted with caution.

Most of the malignancies found during the placebo-controlled portions of the trials were NMSC (70.6%). We performed an analysis omitting all NMSC from the analysis, as there is a potential for unmasking bias for trials including patients with

psoriatic disease as skin cancers may be easier to detect as the psoriasis clears from effective treatment. However, excluding NMSC did not change our results.

The trials included in this meta-analysis were clinically heterogeneous with respect to study drug, trial design, disease indication, previous and concomitant immunosuppressant treatment, and disease duration. However, we found no evidence of statistical heterogeneity for any of our measured outcomes, suggesting that outcomes for the included trials were statistically similar enough to validly pool results across these studies.

The estimated ORs for our outcomes were based on the number of subjects experiencing the events (malignancy, infection) and the number of subjects receiving treatment in each group. As one patient can experience more than one nonserious infection, the rate of nonserious infection and number of patients experiencing at least one nonserious infection may not be equal. In trials where it was not specified whether the number of events instead of the number of subjects experiencing an event was reported,[43,46-51] an assumption of one event per subject was made. For the overall infection analysis, this could have led to an overestimation of effect.

Conclusions

There have been limited studies examining the risk profile of TNF inhibitors in the psoriatic population. The existing literature on risk of infection and malignancy with the use of the TNF-alfa inhibitors from the RA population may not generalize to patients with psoriasis. Of special importance, RA is typically treated with concomitant immunosuppressive therapy whereas psoriasis is not. There is some evidence that there may be a synergistic effect with the use of anti—TNF agents and other immunosuppressants on the risk of infection and malignancy. Thus, compared with the existing literature, our study may provide a more accurate picture of the risks associated with TNF inhibitors when used as monotherapy.

Our results suggest that the short-term risk-to-benefit profile of the TNF-alfa inhibitors in adult patients with psoriatic disease is favorable. However, larger, long-term studies with appropriate control groups will be necessary to fully assess the risk of cancer and serious infection associated with chronic use of TNF inhibitors in the psoriatic population.

REFERENCES

1. Gelfand JM, Feldman SR, Stern RS, Thomas J, Rolstad T, Margolis DJ. Determinants of quality of life in patients with psoriasis: a study from the US population. J Am Acad Dermatol 2004;51:704-8.
2. Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. J Invest Dermatol 2006;126:2194-201.
3. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA 2006;296:1735-41.
4. Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol 2007;143:1493-9.
5. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. J Am Acad Dermatol 2009;60:218-24.
6. Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the general practice research database. Eur Heart J 2010;31:1000-6.
7. Abuabara K, Azfar R, Shin D, Neimann A, Troxel A, Gelfand J. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the United Kingdom. Br J Dermatol 2010;163:586-92.
8. 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.
9. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumor necrosis factor treatments in rheumatoid arthritis: meta and exposure adjusted pooled analyses of serious adverse events. Ann Rheum Dis 2009;68:1136-45.
10. Schiff MH, Burmester GR, Kent JD, Pangan AL, Kupper H, Fitzpatrick SB, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:889-94.
11. Domm S, Cinatl J, Mrowietz U. The impact of treatment with tumor necrosis factor-alpha; antagonists on the course of chronic viral infections: a review of the literature. Br J Dermatol 2008;159:1217-28.
12. Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. Semin Arthritis Rheum 2010;39:327-46.
13. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis Rheum 2005;52:3403-12.
14. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-{alpha} therapy. Rheumatology 2003;42:617-21.
15. Strangfeld A, Listing J, Herzer P, Liebhaber A, Rockwitz K, Richter C, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-{alpha} agents. JAMA 2009;301:737-44.
16. Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, et al. Serious infections during anti-TNFalpha treatment in rheumatoid arthritis patients. Autoimmun Rev 2008;8:266-73.
17. Gómez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD, BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 2003;48:2122-7.
18. Bongartz T, Warren FC, Mines D, Matteson EL, Abrams KR, Sutton AJ. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual

patient data meta-analysis of randomized controlled trials. Ann Rheum Dis 2009;68:1177-83.
19. Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. Clin Gastroenterol Hepatol 2008;6:644-53.
20. Askling J, Fored CM, Baecklund E, Brandt L, Backlin C, Ekbom A, et al. Hematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumor necrosis factor antagonists. Ann Rheum Dis 2005;64:1414-20.
21. Askling J, Baecklund E, Granath F, Geborek P, Fored M, Backlin C, et al. Anti-TNF therapy in RA and risk of malignant lymphomas: relative risks and time-trends in the Swedish biologics register. Ann Rheum Dis 2009;68:648-53.
22. Geborek P, Bladstrom A, Turesson C, Gulfe A, Petersson IF, Saxne T, et al. Tumor necrosis factor blockers do not increase overall tumor risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis 2005;64:699-703.
23. Leonardi CL, Toth D, Cather JC, Langley RG, Werther W, Compton P, et al. A review of malignancies observed during efalizumab (Raptiva®) clinical trials for plaque psoriasis. Dermatology 2006;213:204-14.
24. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheuma 2004;50:1740-51.
25. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheuma 2007;56:2886-95.
26. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum 2007;56:1433-9.
27. Dommasch E, Gelfand JM. Is there truly a risk of lymphoma from biologic therapies? Dermatol Ther 2009;22:418-30.
28. Robinson MR, Korman BD, Korman NJ. Combination immunosuppressive therapies: the promise and the peril. Arch Dermatol 2007;143:1053-7.
29. Gelfand JM. Pharmacovigilance: verifying that drugs remain safe. In: Wolverton SE, editor. Comprehensive dermatologic drug therapy. 2nd ed. Philadelphia (PA): Saunders Elsevier; 2007.
30. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Chichester, England: The Cochrane Collaboration, Wiley, 2008.
31. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264-9.
32. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12.
33. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
34. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719-48.
35. Guevara J, Berlin J, Wolf F. Meta-analytic methods for pooling rates when follow-up duration varies: a case study. BMC Med Res Methodol 2004;4:17.
36. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med 2004;23:1351-75.
37. Light RJ, Pillemer DB. Summing up: the science of reviewing research. Cambridge, MA and London: Harvard University Press, 1984.
38. Song F, Khan KS, Dinnes J, Sutton AJ. Asymmetric funnel plots and publication bias in meta-analyses of diagnostic accuracy. Int J Epidemiol 2002;31:88-95.
39. Sterne JAC, Egger M, Davey Smith G. Investigating and dealing with publication and other biases. In: Egger M, Davey Smith G, Altman DG, eds. Systematic reviews in health care: meta-analysis in context, 2nd ed. London: BMJ Books, 2001.
40. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis 2005;64:1150-7.
41. Ortonne JP, Tasset C, Reich K, Sterry W. Safety and efficacy of subcutaneous certolizumab pegol, a new anti-TNFa monoclonal antibody, in patients with moderate-to-severe chronic plaque psoriasis: preliminary results from a double-blind, placebo-controlled trial; abstract P21. American Academy of Dermatology 65th Annual Meeting, February 2-6, 2007. J Am Acad Dermatol 2007;56:AB6.
42. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al. Etanercept as monotherapy in patients with psoriasis. N Engl J Med 2003;349:2014-22.
43. van de Kerkhof PC, Segaert S, Lahfa M, Luger TA, Karolyi Z, Kaszuba A, et al. Once weekly administration of etanercept 50 mg is efficacious and well tolerated in patients with moderate-to-severe plaque psoriasis: a randomized controlled trial with open-label extension. Br J Dermatol 2008;159:1177-85.
44. Papp KA, Tyring S, Lahfa M, Prinz J, Griffiths CE, Nakanishi AM, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol 2005;152:1304-12.
45. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum 2009;60:976-86.
46. Gordon KB, Langley RG, Leonardi C, Toth D, Menter MA, Kang S, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. J Am Acad Dermatol 2006;55:598-606.
47. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52:3279-89.
48. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. Lancet 2000;356:385-90.
49. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50:2264-72.
50. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. J Am Acad Dermatol 2008;58:106-15.
51. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). Br J Dermatol 2008;158:558-66.
52. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003;139:1627-32.

53. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol 2007;56:31e1-15.
54. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicenter, double-blind trial. Lancet 2005;366:1367-74.
55. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomized phase III trial. Lancet 2006;367:29-35.
56. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum 2005;52:1227-36.
57. Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease-modifying antirheumatic drug therapy. J Rheumatol 2007;34:1040-50.
58. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol 2004;51:534-42.
59. Menter A, Reich K, Gottlieb AB, Bala M, Li S, Hsu MC, et al. Adverse drug events in infliximab-treated patients compared with the general and psoriasis populations. J Drugs Dermatol 2008;7:1137-46.
60. Tyring S, Gordon KB, Poulin Y, Langley RG, Gottlieb AB, Dunn M, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. Arch Dermatol 2007; 143:719-26.
61. Moreland LW, Cohen SB, Baumgartner SW, Tindall EA, Bulpitt K, Martin R, et al. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. J Rheumatol 2001;28: 1238-44.
62. Dixon WG, Symmons DPM, Lunt M, Watson KD, Hyrich KL, British Society for Rheumatology Biologics Register Control Centre Consortium, Silman AJ, British Society for Rheumatology Biologics Register. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum 2007;56:2896-904.
63. Clair EWS, van der Heijde DM, Smolen JS, Maini RN, Bathon JM, Emery P, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: s randomized, controlled trial. Arthritis Rheum 2004;50:3432-43.
64. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (safety trial of adalimumab in rheumatoid arthritis). J Rheumatol 2003;30:2563-71.
65. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum 2004;50:1400-11.
66. Lipsky PE, van der Heijde DMFM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000; 343:1594-602.
67. Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, MacFarlane JD, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41: 1552-63.
68. van de Putte LBA, Atkins C, Malaise M, Sany J, Russell AS, van Riel PLCM, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease-modifying antirheumatic drug treatment has failed. Ann Rheum Dis 2004;63:508-16.
69. van de Putte LBA, Rau R, Breedveld FC, Kalden JR, Malaise MG, van Riel PLCM, et al. Efficacy and safety of the fully human anti-tumor necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis 2003;62:1168-77.
70. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum 2003;48:35-45.
71. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum 2006;54:1075-86.
72. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum 2004;50:1412-9.
73. Weinblatt M, Schiff M, Goldman A, Kremer J, Luggen M, Li T, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomized clinical trial. Ann Rheum Dis 2007; 66:228-34.
74. Weinblatt M, Combe B, Covucci A, Aranda R, Becker JC, Keystone E. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. Arthritis Rheum 2006;54:2807-16.
75. The Wegener's Granulomatosis Etanercept Trial Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352:351-61.
76. Shale M, Kanfer E, Panaccione R, Ghosh S. Hepatosplenic T cell lymphoma in inflammatory bowel disease. Gut 2008;57: 1639-41.
77. Okie S. Safety in numbers—monitoring risk in approved drugs. N Engl J Med 2005;352:1173-6.
78. Akihiko A, Hidemi N, Takafumi E, Mamitaro O. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: efficacy and safety results from a phase II/III randomized controlled study. J Dermatol 2010;37:299-310.