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The Risk of Infection and Malignancy with Tumor Necrosis Factor Antagonists in Adult Patients with Psoriatic Disease: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Abstract

Background—There is a need to better understand the safety of TNF inhibitors in patients with psoriatic disease in whom TNF inhibitors are frequently used as monotherapy.

Objective—Examine the risks of infection and malignancy with the use of TNF antagonists in adult patients with psoriatic disease.

Methods—Systematic search for trials of TNF antagonists for adults with plaque psoriasis (PsO) and psoriatic arthritis (PsA). We included randomized, placebo-controlled trials of etanercept, infliximab, adalimumab, golimumab, and certolizumab for the treatment of PsO and PsA. 20 out of 820 identified studies with a total of 6,810 patients were included. Results were calculated using fixed effects models and reported as pooled odds ratios (OR).

Results—ORs for overall infection and serious infection over a mean of 17.8 weeks were 1.18 (95% 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 OR for malignancy was 1.48 (95% CI: 0.71, 3.09), and 1.26 (95% CI: 0.39, 4.15) when non-melanoma skin cancer was excluded.

Limitations—Short duration of follow-up and rarity of malignancies and serious infections.

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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.

Keywords

psoriasis; psoriatic arthritis; meta-analysis; malignancy; cancer; infection; biologics; safety; TNF-alpha

Classifications

biologics (Rx); biostatistics; clinical trials; controlled trials; epidemiology; infections; immunobiologics; immunosuppression; psoriasis; psoriatic arthritis

INTRODUCTION

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 TNF- α antagonists that suppress inflammatory pathways. These agents are generally safe and well tolerated; however, due to 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 RA or inflammatory bowel disease (IBD). Observational studies and meta-analyses of randomized controlled trials (RCTs) have indicated an increased risk of non-serious 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 RA patients generalizes 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 IBD 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. Additionally, open-label extension trials and post-marketing surveillance databases often lack adequate control groups and spontaneous reports are generally not reliable for assessing malignancy and infection risk due to severe underreporting.²⁹ In this study, we sought to evaluate the risk of malignancy, serious infection, and non-serious infection associated with the use of anti-TNF- α agents in adult patients with plaque psoriasis and psoriatic arthritis by conducting a meta-analysis of RCTs.

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 plaque psoriasis (PsO) and psoriatic arthritis (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 30th, 2009 using the terms *psoriasis*, *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 unique 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, adalimumab, golimumab), and 1 anti-TNF agent currently under investigation (certolizumab) for the treatment of adult patients with moderate to severe PsO and/or PsA, 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 Jadad scale³², 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.) for our two primary outcomes of malignancy and infection, with disagreement resolved by consensus. We additionally classified infections as serious or non-serious. Serious infection was defined as an infection that was considered a serious adverse event (SAE), and non-serious infection as an infection that was not recorded as an SAE by study investigators. We classified reported malignancies as non-melanoma 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 and/or industry sponsors. All industry sponsors as well as 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.

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 1 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 methods³⁴ 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 confidence intervals.³⁰ We calculated ORs across all included studies, and additionally performed subanalyses by indication and drug. We calculated a number needed to harm (NNH) based on the Mantel-Haenszel fixed effects model estimate if the OR was statistically significant.

We additionally 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 (e.g. 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 additionally 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 1 study at a time. We used funnel plots to evaluate the potential for publication bias with respect to our primary endpoints (malignancy and infection).^{30, 37–39} We also used the Egger test to evaluate the risk of publication bias, with a 2-tailed P value of less than 0.05 considered to be statistically significant.³⁰

All analyses were performed using Stata version 10.0 (StataCorp, College Station, Texas) 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 6,810 adult patients (5,427 patients in PsO and 1,383 patients in PsA studies) qualified for inclusion (Figure 1). Seven trials specifically included patients with active PsA unresponsive to DMARDs and/or non-steroidal anti-inflammatory drugs (NSAIDs), although five of these trials additionally required that patients have active psoriatic skin lesions and/or a documented history of PsO. 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 2 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 4,598 patients included in the treatment group and 2,313 patients included in the placebo group for the meta-analysis (see Table 1 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 percent, $p = 0.005$). According to the published manuscripts, the greater withdrawal rate in the placebo group was largely due to 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 Jadad criteria.^{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, $p = 0.0004$), partially due to differential drop out between the placebo and treatment groups, but additionally because many trials included multiple treatment groups for different doses of study drug (see Table 1). 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, 1 squamous cell carcinoma, 1 prostate cancer, and 1 breast cancer) in the treatment group and 2 malignancies (2 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 2).

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 ($I^2 = 0.0\%$, $p = 0.91$). We also conducted subanalyses by drug (see Figure 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 the 24-weeks. In another trial by Antoni et al. of infliximab,⁴⁰ only one malignancy occurred in the trial in a patient receiving placebo.

Overall, 70.6% of malignancies included in our analysis were non-melanoma skin cancers (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 non-serious). Several studies (n = 7)^{43, 46–51} did not specify whether reported non-serious infections were by number of events or by number of patients experiencing at least 1 non-serious infection. For non-serious infections, four 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 2).

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 non-serious, i.e., not recorded as an SAE. The ORs were 1.22 (1.06, 1.40) for PsO trials and 1.09 (0.87, 1.37) for PsA trials when separating by indication. We also stratified the risk of infection by drug (see Figure 3). The NNH for treatment with all anti-TNF agents was 29. There was no evidence of statistically significant heterogeneity ($I^2 = 21.6\%$, $p = 0.187$). The estimated OR for non-serious 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 patient-years, the IRR for overall infection was 1.01 (95% CI: 0.92, 1.11) and 0.59 (95% CI: 0.35, 0.99) for serious infection. The estimated IRR for non-serious infection was 1.02 (95% CI: 0.93, 1.13).

Publication Bias

We found no evidence of publication bias with Egger tests for malignancy ($P = 0.54$), NMSC ($p = 0.29$), malignancies excluding NMSC ($p = 0.48$), overall infection ($p = 0.18$), non-serious infection ($p = 0.16$), or serious infection ($p = 0.14$). Funnel plots were also created for the above outcomes, all of which were found to be symmetrical.

DISCUSSION

Our systematic review and meta-analysis combined data from 20 RCTs of adult patients with plaque psoriasis and psoriatic arthritis treated with anti-TNF- α 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- α 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-alpha antagonists for psoriatic disease. However, 97.6% of reported infections were non-serious, 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 patient-years 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 to 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 prior to 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, which 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).⁸ This meta-analysis included 9 randomized controlled trials, 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. than 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 per 100 patient-years, 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 Bongartz analysis was longer than those included in our study (mean of 32.7, range 12–54 weeks compared to 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 Additionally, the large majority of malignancies reported in the study by Bongartz et al. occurred within the first 24 weeks (25 vs. 8 occurring at >24 weeks).¹⁸

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. (n = 5005),⁸ approximately 77.1% of the patients were on MTX, 6.5% were on other DMARDs, 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 MTX, 5.5% were on other DMARDs, 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-alpha 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. Due to the rarity of events and short duration of follow-up, the confidence intervals we calculated for malignancy and serious infection were wide and do not rule out potential associations that could be clinically significant. Moreover,

safety endpoints were grouped (e.g. serious infections, malignancy) and therefore, this analysis could not determine the risk of specific individual outcomes such as tuberculosis or lymphoma. Additionally, 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 in order to accurately define risk. In general, side effects which are delayed in onset or occur at a rate of <1 in 1000 patients per year are often only recognized after a medication is in widespread use, with over half of medications entering the market having serious adverse events discovered only after FDA approval. Thus, it has been suggested that a novel drug should have at least 20,000 patients exposed with direct observation (i.e., 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. Since 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, while 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 non-serious infection, the rate of non-serious infection and number of patients experiencing at least 1 non-serious 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-alpha inhibitors from the RA population may not generalize to psoriatic patients. Of special importance, RA is typically treated with concomitant immunosuppressive therapy while 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 to 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-alpha 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.

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Abbreviations and Acronyms

PsO	plaque psoriasis
PsA	psoriatic arthritis
RCT	randomized, controlled trial
RA	rheumatoid arthritis
IBD	irritable bowel disease
TNF	tumor necrosis factor
SAE	serious adverse event
NMSC	non-melanoma skin cancer
DMARD	disease-modifying antirheumatic drug
OR	odds ratio
IRR	incidence rate ratio
NNH	number needed to harm
NSAIDS	non-steroidal anti-inflammatory drugs
EOW	every other week

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Figure 1.
Selection of Studies for Meta-analysis

Figure 2.
Odds Ratio (OR) of Malignancy Associated with Anti-TNF Treatment vs Control

Figure 3.
Odds Ratio (OR) of Overall Infection Associated with Anti-TNF Treatment vs Control

Table 1

Trial Characteristics

		Treatment Group (n = 4598)				Placebo Group (n = 2313)			
Source	Trial Name/Registry Number	Disease Indication ^a	Permitted Concomitant Systemic Therapy ^b	Duration of Placebo-Controlled Trial, wks	Treatment (Dose) ^c	No. of Patients	Patient-years follow-up	No. of Patients	Patient-years follow-up
Mease et al, 200547	Study M02-518 / NCT00646386	PsA	MTX (≤30 mg/wk) or prednisone (≤10 mg/day) at stable dose; rescue therapy after 12 wks with DMARDS or corticosteroids	24	Adalimumab (40 mg eow)	151	66.8	162	71.1
Gordon et al, 200646	Study M02-528 / NCT00645814	PsO	None	12	Adalimumab (40 mg eow) Adalimumab (40 mg weekly)	45 50	10.2 11.2	52	11.8
Genovese et al, 200757	Study M02-570 / NCT00646178	PsA	MTX (≤30 mg/wk) or prednisone (≤10 mg/day), or other DMARD at stable dose	12	Adalimumab (40 mg eow)	51	11.8	49	10.8
Menter et al, 200850	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, 200851	CHAMPION / Study M04-716 / NCT00235820	PsO	None	16	Adalimumab (80 mg at wk 0, then 40 mg eow starting at wk 1) MTX (7.5 mg, increased as needed and as tolerated to 25 mg weekly) ^d	108 110	34.7 34.8	52	16.3
Akihiko et al, 2011078	Study M04-688 / NCT00338754	PsO	None	24	Adalimumab (80 mg at wk 0, then 40 mg eow starting at wk 1) Adalimumab (40 mg eow) Adalimumab (80 mg eow)	38 43 42	16.3 17.2 17.9	46	19.1
Unpublished41	Study C87040 / NCT00245765	PsO	None	12	Certolizumab pegol (400 mg at wk 0, then 200 mg every 2 wks) Certolizumab pegol (400 mg every 2 wks)	59 58	Unknown	59	Unknown
Mease et al, 200048	Study 20021630	PsA and PsO	MTX (≤25 mg/wk) or prednisone (≤10 mg/day) at stable dose	12	Eianercept (25 mg twice weekly)	30	6.5	30	6.1
Gottlieb et al, 200352	Study 20021632	PsO	None	24	Eianercept (25 mg twice weekly)	57	23.6	55	14.5
Leonardi et al, 200342	Study 20021639	PsO	None	12	Eianercept (25 mg weekly) Eianercept (25 mg twice weekly) Eianercept (50 mg twice weekly)	160 162 164	34.3 34.6 35.8	166	34.9
Mease et al, 200449	NCT00317499	PsA	MTX (≤25 mg/wk) or prednisone (≤10 mg/day) at stable dose	24	Eianercept (25 mg twice weekly)	101	81.0	104	59.2

Source	Trial Name/Registry Number	Disease Indication ^a	Permitted Concomitant Systemic Therapy ^b	Duration of Placebo-Controlled Trial, wks	Treatment Group (n = 4598)			Placebo Group (n = 2313)		
					Treatment (Dose) ^c	No. of Patients	Patient-years follow-up	No. of Patients	Patient-years follow-up	Patient-years follow-up
Papp et al, 200544	Study 20021642	PsO	None	12	Etanercept (25 mg twice weekly) Etanercept (50 mg twice weekly)	196 194	42.9 42.6	193	41.0	41.0
Tyring et al, 200755	NCT00111449	PsO	None	12	Etanercept (50 mg twice weekly)	312	68.8	306	65.9	65.9
van de Kerkhof et al, 200843	NCT00333034	PsO	None	12	Etanercept (50 mg weekly)	96	Unknown	46	Unknown	Unknown
Kavanaugh et al, 200945	NCT00265096	PsA	Stable dose of MTX, prednisone, or NSAIDS	24 with early escape at week	Golimumab (50 mg every 4 wks) Golimumab (100 mg every 4 wks) All golimumab ^e	146 146 343	62 67 142	113	42	42
Gottlieb et al, 200458	SPIRIT / NCT00230529	PsO	NSAIDS	30	Infliximab (3 mg/kg at wks 0, 2, 6) Infliximab (5 mg/kg at wks 0, 2, 6)	98 99	56 58	51	20.5	20.5
Antoni et al, 200556	IMPACT	PsA	MTX or other DMARD at stable dose	16	Infliximab (5 mg/kg at wks 0, 2, 6, 14)	52	16	51	16	16
Antoni et al, 200540	IMPACT 2 / NCT00051623	PsA	MTX (≤25 mg/wk) or prednisone (≤10 mg/day) at stable dose	24 with early escape at wk 16	Infliximab (5 mg/kg at wks 0, 2, 6, 14, 22) All infliximab ^f	100 150	45 53	97	37	37
Reich et al, 200554	EXPRESS I / NCT00106834	PsO	NSAIDS	24	Infliximab (5 mg/kg at wks 0, 2, 6, 14, 22)	298	135	76	33	33
Menter et al, 200753	EXPRESS II / NCT00106847	PsO	NSAIDS	14	Infliximab (3 mg/kg at wks 0, 2, 6) Infliximab (5 mg/kg at wks 0, 2, 6)	313 314	85 85	207	54	54

^aPsA = psoriatic arthritis; PsO = plaque psoriasis

^bMTX = methotrexate; DMARDS = disease-modifying antirheumatic drugs; NSAIDS = non-steroidal anti-inflammatory drugs

^ccow = every other week

^dNot included in meta-analysis.

^eAll golimumab group includes all patients who received at least one dose of study drug.

^fAll infliximab group includes all those that received at least one dose of study drug.

Table 2
Malignancies and Infectious Events Occurring in Randomized Controlled Trials^a

Source	Treatment (Dose) ^b	Treatment Group (n = 4598)					Placebo Group (n = 2313)				
		No. of Pts	Pts with ≥ 1 Serious Infection	Pts with ≥ 1 Infectious Event	No. of Malignancy ^c	Type of Malignancy ^d	No. of Pts	Pts with ≥ 1 Serious Infection	Pts with ≥ 1 Infectious Event	No. of Malignancy	Type of Malignancy
Mease et al, 200547	Adalimumab (40 mg eow)	151	1	68	0		162	1	64	0	
Gordon et al, 200646	Adalimumab (40 mg eow)	45	0	5	1	Metastatic SCC ^e	52	0	8	0	
	Adalimumab (40 mg weekly)	50	1	13	1	Breast Cancer	5.1				
Genovese et al, 200757	Adalimumab (40 mg eow)	51	0	9	0		49	1	16	0	
Menter et al, 200850	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	398	4	89	2	NMSC Uterine- carcinoma
Saurat et al, 200851	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, 201078	Adalimumab (80 mg at wk 0, then 40 mg eow starting at wk 1)	38	0	21	0		46	0	23	0	
	Adalimumab (80 mg at wk 0, then 40 mg eow starting at wk 1)	43	0	18							
	Adalimumab (40 mg eow)	42	0	21							
Unpublished41	Certolizumab pegol (400 mg at wk 0, then 200 mg every 2 wks)	59	1	16	0		59	0	24	0	
	Certolizumab pegol (400 mg every 2 wks)	58	2	27							
Mease et al, 200048	Etanercept (25 mg twice weekly)	30	0	17 ^f	0		30	0	17 ^f	0	
Gottlieb et al, 200352	Etanercept (25 mg twice weekly)	57	0	28 ^g	0		55	1	14 ^g	0	
Leonardi et al, 200342	Etanercept (25 mg weekly)	160	2	18 ^g	1	BCC	166	2	22 ^g	2	SCC × 2
	Etanercept (25 mg twice weekly)	162	0	15	0	BCC	11.6				0.7, 1.9
	Etanercept (50 mg twice weekly)	164	1	10	2	Prostate Cancer	9.1				
Mease et al, 200449	Etanercept (25 mg twice weekly)	101	0	33	0		104	1	39	0	

Source	Treatment (Dose) ^b	Treatment Group (n = 4598)					Placebo Group (n = 2313)				
		No. of Pts	Pts with ≥ 1 Serious Infection	Pts with ≥ 1 Infectious Event	No. of Malignancy ^c	Type of Malignancy ^d	No. of Pts	Pts with ≥ 1 Serious Infection	Pts with ≥ 1 Infectious Event	No. of Malignancy	Type of Malignancy
Papp et al, 200544	Etanercept (25 mg twice weekly) Etanercept (50 mg twice weekly)	196 194	1 0	36 ^h 35	0 4	Breast Cancer SCC BCC × 2	193	1	29 ^h	0	
Tyring et al, 200755	Etanercept (50 mg twice weekly)	312	1	88	3	SCC BCC Pancreatic- Carcinoma	306	1	71	1	Bladder- carcinoma
van de Kerkhof et al, 200843	Etanercept (50 mg weekly)	96	0	27	0		46	0	12	0	
Kavanaugh et al, 200945	Golimumab (50 mg every 4 wks) Golimumab (100 mg every 4 wks) All Golimumab ⁱ	146 146 343	1 1 2	48 60 118	0 3 3	BCC × 2 Prostate cancer As above	113	4	27	0	
Gottlieb et al, 58	Infliximab (3 mg/kg at wks 0, 2, 6) Infliximab (5 mg/kg at wks 0, 2, 6)	98 99	0 1	31 37	2 1	SCC × 2 BCC	51	0	11	0	
Antoni et al, 200556	Infliximab (5 mg/kg at wks 0, 2, 6, 14)	52	1	6	0		51	0	9	0	
Antoni et al, 200540	Infliximab (5 mg/kg wks 0, 2, 6, 14, 22) All Infliximab ^c	100 150	3 3	34 47	0 0		97	2	29	1	BCC
Reich et al, 54	Infliximab (5 mg/kg wks 0, 2, 6, 14, 22)	298	3	125	2	SCC BCC	76	0	30	0	
Menter et al, 200753	Infliximab (3 mg/kg at wks 0, 2, 6) Infliximab (5 mg/kg at wks 0, 2, 6)	313 314	0 1	106 97	1 1	BCC BCC	207	1	62	0	

^a A total of 9 malignancies (in bold) were unpublished and obtained from industry sponsors.

^b Eow = every other week

^c Malignancy = malignancy

^d SCC = Squamous cell carcinoma; BCC = Basal cell carcinoma; NMSC = non-melanoma skin cancer (unspecified)

^e Non-cutaneous metastatic SCC on the left side of the neck. Swollen lymph node on the left side of the neck was present at screening.

f Only upper respiratory tract events reported.

g Only upper respiratory tract infections (URIs) and sinusitis reported.

h Only URIs and flu syndrome reported.

i Early escape at week 16. All malignancies occurred in patients receiving only the 100 mg dose