REVIEW

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

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Context Tumor necrosis factor (TNF) plays an important role in host defense and tumor growth control. Therefore, anti-TNF antibody therapies may increase the risk of serious infections and malignancies.

Objective To assess the extent to which anti-TNF antibody therapies may increase the risk of serious infections and malignancies in patients with rheumatoid arthritis by performing a meta-analysis to derive estimates of sparse harmful events occurring in randomized trials of anti-TNF therapy.

Data Sources A systematic literature search of EMBASE, MEDLINE, Cochrane Library, and electronic abstract databases of the annual scientific meetings of both the European League Against Rheumatism and the American College of Rheumatology was conducted through December 2005. This search was complemented with interviews of the manufacturers of the 2 licensed anti-TNF antibodies.

Study Selection We included randomized, placebo-controlled trials of the 2 licensed anti-TNF antibodies (infliximab and adalimumab) used for 12 weeks or more in patients with rheumatoid arthritis. Nine trials met our inclusion criteria, including 3493 patients who received anti-TNF antibody treatment and 1512 patients who received placebo.

Data Extraction Data on study characteristics to assess study quality and intention-to-treat data for serious infections and malignancies were abstracted. Published information from the trials was supplemented by direct contact between principal investigators and industry sponsors.

Data Synthesis We calculated a pooled odds ratio (Mantel-Haenszel methods with a continuity correction designed for sparse data) for malignancies and serious infections (infection that requires antimicrobial therapy and/or hospitalization) in anti-TNF–treated patients vs placebo patients. We estimated effects for high and low doses separately. The pooled odds ratio for malignancy was 3.3 (95% confidence interval [CI], 1.2-9.1) and for serious infection was 2.0 (95% CI, 1.3-3.1). Malignancies were significantly more common in patients treated with higher doses compared with patients who received lower doses of anti-TNF antibodies. For patients treated with anti-TNF antibodies in the included trials, the number needed to harm was 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (95% CI, 39-125) within a treatment period of 3 to 12 months.

Conclusions There is evidence of an increased risk of serious infections and a dose-dependent increased risk of malignancies in patients with rheumatoid arthritis treated with anti-TNF antibody therapy. The formal meta-analysis with pooled sparse adverse events data from randomized controlled trials serves as a tool to assess harmful drug effects.

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IT IS UNCERTAIN TO WHAT EXTENT therapy with anti–tumor necrosis factor (anti-TNF) agents for rheumatoid arthritis (RA) might be associated with an increase in serious infections and malignancies. This uncertainty is based on the difficulties that generally emerge from the analysis and interpretation of sparse adverse event data derived from randomized controlled trials, which have not been powered to detect rare adverse effects. In addition, postlicensure observational studies usually lack an adequate control group, leaving open to interpretation whether events are associated with the therapeutic agent or with the disease itself.

Two types of anti-TNF antibodies currently licensed for clinical use in RA are infliximab and adalimumab, the former being a partially and the latter a fully humanized monoclonal antibody specific for TNF. They neutralize both extracellular and membrane forms of TNF, a cytokine considered to be of major importance in the pathophysiology of RA.[1]

Basic science research suggests that infectious complications and malignancies should be seriously consid-

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ered as possible adverse effects of TNF antagonists. Animal models indicate an essential role of TNF in combating infection.[2-4] In addition, TNF is important in natural killer cell– and CD8 lymphocyte–mediated killing of tumor cells, although tumor-promoting effects of TNF have also been described.[5] Randomized trials in patients with RA have been inconsistent, with some showing significant[6,7] and others no significant association[8-11] between serious infections and use of anti-TNF therapy. Postmarketing surveillance and observational studies have suggested an increased risk of serious infections with anti-TNF therapies.[12-14]

Malignancies reported in randomized trials of anti-TNF therapy for RA are rare, and observed differences in their occurrence between groups have not been statistically significant. A prospective cohort study comparing patients treated with anti-TNF therapies vs patients receiving methotrexate or no disease-modifying antirheumatic drugs (DMARDs) suggested an increased risk of hematological malignancies in anti-TNF–treated patients.[15] Because randomized trials have been too small or too brief to accumulate enough adverse events, and because postlicensure observational studies usually lack an adequate control group that would allow stronger causal inferences (particularly in the face of an already increased risk of infection and certain malignancies in patients with RA[16-18]), at this time, the extent to which anti-TNF therapies increase the risk of malignancy and serious infections in patients with RA remains unclear.

One solution to the lack of precision in the estimates of harm derived from individual randomized trials is to pool their results using meta-analysis. Although this technique is commonly used as a powerful tool to assess drug efficacy, meta-analysis is rarely used to assess harmful effects. We conducted such an analysis while applying a validated technique for pooling sparse event data as a tool for complementing the evaluation of drug safety.[19]

METHODS

Study selection, assessment of eligibility criteria, data extraction, and statistical analysis were performed based on a predefined, peer-reviewed protocol according to the Cochrane Collaboration guidelines (http://www.cochrane.org/resources/handbook/index.html).

This article was prepared in accordance with the QUOROM statement.[20]

Data Sources and Search Strategy

We searched EMBASE, MEDLINE, and the Cochrane Library from inception to December 2005 using the terms *arthritis, rheumatoid*; *biological products/therapeutic use*; *infliximab*; *adalimumab*; *D2E7*; *cA2*; *randomized controlled trial*; *random allocation*; *multicenter studies*; *clinical trials, phase II*; *clinical trials, phase III*; and *clinical trials, phase IV*.

To locate unpublished trials, we searched the electronic abstract databases of the annual scientific meetings of both the European League Against Rheumatism and the American College of Rheumatology from 1996 to present. In addition, both manufacturers (Centocor, Horsham, Pa, and Abbott Laboratories, Abbott Park, Ill) of the 2 licensed anti-TNF antibodies studied were contacted regarding information on unpublished trials.

Assessment of eligibility criteria for inclusion or exclusion and extraction of outcome variables was performed independently by 2 investigators (T.B. and E.L.M.). Disagreements were resolved by consensus.

Selection and Outcomes

We included randomized trials of the 2 currently licensed anti-TNF antibodies, infliximab and adalimumab, in which patients were treated who were classified as having RA according to American College of Rheumatology criteria.[21] Study participants had to be randomized to receive treatment with an anti-TNF antibody vs placebo (or anti-TNF antibody plus traditional DMARD vs placebo plus traditional DMARD) for at least 12 weeks.

Data Abstraction and Study Validity Assessment

Data were abstracted for the following 2 outcomes: serious infection, defined as infection that requires antimicrobial therapy or hospitalization; and malignancies, defined as a group of diseases characterized by abnormal cells that divide without control and have the ability to invade other tissues. Primary data sources were the published versions of the identified trials. In addition, we searched the pertinent US Food and Drug Administration (FDA) database (http://www.fda.gov) to verify the data provided in the published data. All principal investigators and sponsors were contacted to verify the reported numbers of malignancies and serious infections and to obtain information on the type and time point of occurrence of all malignancies.

The following methodological features of all trials most relevant to the prevention of bias were evaluated by 2 independent reviewers (T.B. and E.L.M.), with disagreement resolved by consensus: randomization, allocation concealment, masking of allocation, intention-to-treat analysis, completeness of follow-up, outcome assessment, and attrition.

Statistical Analysis

Based on the adverse event analysis in each trial, we determined the number of patients with at least 1 serious infection or malignancy. The number of patients who received at least 1 dose of the study drug represented the denominator of our outcome measure.

Our protocol called for a fixed-effects meta-analysis because of its superior performance when pooling trials with few or no events compared with the random-effects model, with results expressed as odds ratios (ORs) and associated 95% confidence intervals (CIs).[19] Based on the OR for each individual trial comparing all anti-TNF–treated patients with placebo patients, we calculated a pooled estimate using Mantel-Haenszel methods with a Robins-Breslow-Greenland variance.[22]

Because we observed zero-event data in some groups and imbalances in patient numbers between study arms (median ratio, 3:1; maximum ratio, 6:1), we used a continuity correction when there were no events observed in 1 study arm of a trial. This correction was inversely proportional to the relative size of the opposite of the study. For example, the continuity correction for the treatment arm was 1/(R + 1), where R is the ratio of control group to treatment group sizes. Similarly, the continuity correction for the control arm was R/(R + 1). Sweeting et al[19] have demonstrated that this approach generally outperforms the use of a constant continuity correction of 0.5 in the setting of sparse event data and imbalanced study arms. We measured inconsistency across trials using the I^2 statistic; results range between 0% (ie, no observed heterogeneity) and 100%. High values reflect increasing heterogeneity.[23,24]

To detect a potential difference in the frequency of the 2 serious adverse events between patients treated with higher doses of anti-TNF antibodies and those who received lower doses, we calculated pooled estimates according to 2 separate and a priori–defined dose groups (low-dose group: ≤3 mg/kg of infliximab every 4 weeks or 20 mg of adalimumab weekly; high-dose group: ≥6 mg/kg of infliximab every 8 weeks or 40 mg of adalimumab every other week).

Sensitivity analyses involved the exclusion of trials with moderate or high risk of bias, omission of malignancies diagnosed within the first 6 weeks of a trial, and omission of malignancies that were classified as nonmelanoma skin cancers. Furthermore, a statistical sensitivity analysis was performed using Mantel-Haenszel methods without a continuity correction, a Gibbs sampler Bayesian fixed- and random-effects model (based on logistic regression) with and without inclusion of trials with zero events in both treatment arms, and a conditional maximum likelihood approach for generation of a pooled estimate (technical details of the models fitted to the data are available on request from the authors). S-PLUS, version 7 (Insightful Corp, Seattle, Wash), WinBUGS, version 1.4 (MRC, Cambridge, England), and StatsDirect, version 2.5.3 (StatsDirect Ltd, Cheshire, England) statistical software were used for calculations and generation of forest plots.

To provide a more useful measure for medical practice, the number needed to harm was calculated based on the Mantel-Haenszel fixed-effects estimate of the absolute risk difference in cases in which an OR of at least 1.5 was detected.

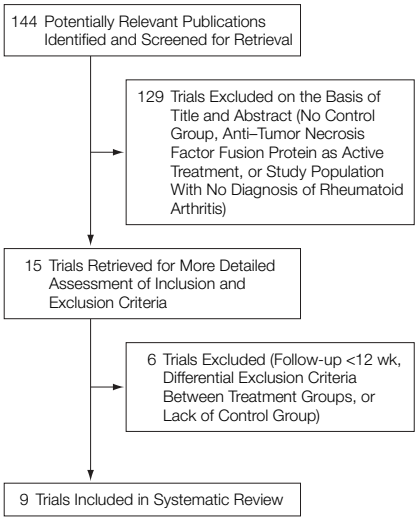
RESULTS

Search Results and Trial Characteristics

Of 144 potentially relevant publications retrieved during our initial search, 129 were excluded based on lack of a randomized controlled trial design, missing control groups, TNF blockade with molecules other than antibodies, and study populations other than patients with RA. A total of 15 trials were evaluated in a detailed assessment. Of these, 6 retrieved trials[25-30] were not eligible due to inadequate treatment duration, differential entry/exclusion criteria between treatment groups, and lack of a control group (FIGURE 1). We could not obtain complete data for 1 trial that was only available as a poster abstract.[31] Nine trials were eligible for inclusion in our analysis.[6-11,32-34] In all selected trials, patients and observers were masked to treatment allocation. Results of 1 included trial have been reported only as a poster abstract, but the sponsor provided all necessary data to evaluate study quality and adverse events.[34]

Assessment of study validity revealed some potential sources of bias. 4 trials reported a higher number of withdrawals due to inefficacy in the placebo groups. Higher numbers of infusion or allergic skin reactions in the anti-TNF treatment arms were observed in all trials and carried a risk of partial unmasking of treatment allocation. One trial[8] showed clinically significant differences between treatment arms concerning the number and type of concomitant DMARDs after randomization at baseline. Only 2 trials reported on the loss of randomized patients to follow-up during the trial period (0.4%[33] and 1.1%,[6] respectively).

Figure 1. Meta-analysis Study Selection



Included trials were somewhat heterogeneous in terms of included patients and concomitant drug use. Eight trials included patients with high disease activity despite treatment with a traditional DMARD. One trial included patients with early RA, with high disease activity and a disease duration of less than 3 years.[7] TABLE 1 describes the characteristics of all included trials.

Patients

Overall, 5014 patients with RA were randomized to receive either anti-TNF antibody or a control treatment. In 2 trials, the number of randomized patients did not equal the number of patients who received at least 1 dose of the study drug. One trial[9] reported 2 patients who erroneously received an infliximab infusion although assigned to the placebo group and, thus, were included in an infliximab treatment arm for safety analysis (3 mg/kg every 8 weeks). Another trial[7] reported 9 randomized patients who did not receive at least 1 dose of the

study drug and were excluded from the safety analysis.

Malignancies

Published data in the 9 retrieved randomized controlled trials reported 24 malignancies in 3493 patients who received at least 1 dose of an anti-TNF antibody (0.8%) and 2 malignancies in 1512 control patients (0.2%). Safety data from these trials as reported to the FDA included 37 malignancies in the treatment groups and 3 malignancies in the control groups. After contacting the sponsors and principal investigators for verification of the retrieved numbers and clarification of discrepancies between published and FDA data, 29 malignancies in the treatment groups and 3 malignancies in the placebo groups were used for analysis (TABLE 2). Seven malignancies not reported in the published data were skin cancers (2 squamous cell carcinoma and 5 basal cell carcinoma) and 6 malignancies were malignant lymphoma that occurred in the anti-TNF study arms during follow-up, after the actual trial period had ended. The latter were not included in this meta-analysis. Two malignancies, which occurred in 2 anti-TNF–treated patients who had already developed a first malignancy during the study period, were censored and not included into the analysis.

Our measure of inconsistency between trials (I^2) was 0% (95% CI, 0%-25%), indicating that studies were not statistically heterogeneous.

Combining the individual ORs of studies with at least 1 event in any group, the pooled OR for malignancies in patients with RA using anti-TNF drugs vs placebo patients was 3.3 (95% CI, 1.2-9.1) (FIGURE 2).

Estimates remained statistically significant when applying the Mantel-

Table 1. Characteristics of Randomized Controlled Trials Included in the Meta-analysis

Source	No. of Randomized Participants	Disease Characteristics	Active Treatment Group (No. of Participants*)	Control Group (No. of Participants*)	Duration of Trial, wk
Maini et al,[32] 1998	101	Active RA with inadequate response to methotrexate	Placebo + 1 mg/kg infliximab every 4 wk (14) Methotrexate + 1 mg/kg infliximab every 4 wk (15) Placebo + 3 mg/kg infliximab every 4 wk (15) Methotrexate + 3 mg/kg infliximab every 4 wk (14) Placebo + 10 mg/kg infliximab every 4 wk (14) Methotrexate + 10 mg/kg infliximab every 4 wk (15)	Placebo + methotrexate (14)	26 (Last dose at wk 14)
Lipsky et al,[9] 2000	428	Active RA with inadequate response to methotrexate	Methotrexate + 3 mg/kg infliximab every 8 wk (88)† Methotrexate + 3 mg/kg infliximab every 4 wk (86) Methotrexate + 10 mg/kg infliximab every 8 wk (87) Methotrexate + 10 mg/kg infliximab every 4 wk (81)	Methotrexate + placebo (86)†	54
Furst et al,[8] 2003	636	Active RA	Adalimumab, 40 mg every other wk + DMARD (318) Rescue arm after 12 wk	Placebo + DMARD (318) Rescue arm after 12 wk	24
Van de Putte et al,[10] 2003	284	Active RA with inadequate response to ≥1 DMARD	Adalimumab, 20 mg/wk (72) Adalimumab, 40 mg/wk (70) Adalimumab, 80 mg/wk (72)	Placebo (70)	12
Weinblatt et al,[11] 2003	271	Active RA with inadequate response to methotrexate	Methotrexate + 20 mg adalimumab every other wk (69) Methotrexate + 40 mg adalimumab every other wk (67) Methotrexate + 80 mg adalimumab every other wk (73) Rescue arm after 16 wk	Methotrexate + placebo (62) Rescue arm after 16 wk	24
Keystone et al,[6] 2004	619	Active RA with inadequate response to methotrexate	Methotrexate + 20 mg adalimumab weekly (212) Methotrexate + 40 mg adalimumab every other wk (207) Rescue arm after 16 wk	Methotrexate + placebo (200) Rescue arm after 16 wk	52
St Clair et al,[7] 2004	1049	Active early RA <3 y (no previous methotrexate)	Methotrexate + 3 mg/kg infliximab every 8 wk (372)‡ Methotrexate + 6 mg/kg infliximab every 8 wk (377)‡	Methotrexate + placebo (291)‡	54
Van de Putte et al,[33] 2004	544	Active RA with inadequate response to ≥1 DMARD	Adalimumab, 20 mg every other wk (106) Adalimumab, 20 mg/wk (112) Adalimumab, 40 mg every other wk (113) Adalimumab, 40 mg/wk (103) Rescue arm after 8 wk	Placebo (110) Rescue arm after 8 wk	26
Westhovens et al,[34] 2004	1082	Active RA with inadequate response to methotrexate	Methotrexate + 3 mg/kg infliximab at wk 0, 2, 6, and 14 (360) Methotrexate + 10 mg/kg infliximab at wk 0, 2, 6, and 14 (361)	Methotrexate + placebo (361)	22

Abbreviations: DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis.
*Numbers of participants who received at least 1 dose of the study drug are shown in parentheses.
†Two patients who were supposed to receive placebo inadvertently received an infliximab infusion and were included in an infliximab treatment arm for safety analysis.
‡Nine randomized patients did not receive at least 1 dose of the study drug.

Haenszel methods without a continuity correction (OR, 4.1; 95% CI, 1.3-13.4), when using the Bayesian fixed-effect model with (OR, 4.8; 95% CI, 1.61-22.03) and without (OR, 4.9; 95% CI, 1.7-19.5) inclusion of trials with zero events in both treatment arms, and when using the conditional maximum likelihood approach (OR, 4.4; 95% CI, 1.3-22.8). Furthermore, with a Bayesian random-effects analysis, we yielded an OR of 7.91 (95% CI, 1.29-1652.0), which did not change after inclusion of trials with zero events in both treatment arms (OR, 7.46; 95% CI, 1.32-1492). Omission of malignancies diagnosed within the first 6 weeks of a trial and omission of all nonmelanoma skin cancers did not change our pooled estimate, yielding ORs of 4.5 (95% CI, 1.3-15.8) and 3.7 (95% CI, 1.0-13.2), respectively.

Subgroup analysis of trials that used high- and low-dose groups of anti-TNF treatment revealed a consistent and significant difference of the pooled estimate between dose groups, obtaining an OR of 4.3 (95% CI, 1.6-11.8) for high-dose anti-TNF vs placebo, an OR of 1.4 (95% CI, 0.3-5.7) for low-dose anti-TNF vs placebo, and an OR of 3.4 (95% CI, 1.4-8.2) for the comparison of high-dose group vs low-dose group.

Table 2. Summary of Malignancies in Randomized Controlled Trials*

	Anti-TNF–Treated Participants (n = 3493)			Controls (n = 1512)	
Source	Type of Malignancy Among Patients With ≥1 Malignancy	Dosage	Time of Diagnosis, wk	Type of Malignancy Among Patients With ≥1 Malignancy	Time of Diagnosis, wk
Maini et al,[32] 1998	0			0	
Lipsky et al,[9] 2000	1 Lymphoma	Infliximab, 10 mg every 4 wk	26	0	
	1 Rectal carcinoma	Infliximab, 10 mg every 8 wk	26		
	1 Breast cancer	Infliximab, 10 mg every 4 wk	19		
	1 Malignant melanoma + squamous cell carcinoma	Infliximab, 10 mg every 4 wk	26		
	1 Basal cell carcinoma + recurrence	Infliximab, 10 mg every 8 wk	8		
Furst et al,[8] 2003	1 Basal cell carcinoma†	Adalimumab, 40 mg every other wk	3	0	
	1 Lymphoma (T cell)	Adalimumab, 40 mg every other wk	9		
	1 Basal cell carcinoma†	Adalimumab, 40 mg every other wk	10		
	1 Basal cell carcinoma†	Adalimumab, 40 mg every other wk	19		
	1 Lymphoma (large B cell)†‡	Adalimumab, 40 mg every other wk	38		
	1 Lymphoma (large B cell)†‡	Adalimumab, 40 mg every other wk	97		
Van de Putte et al,[10] 2003	0			0	
Weinblatt et al,[11] 2003	1 GI adenocarcinoma	Adalimumab, 80 mg every other wk	18	0	
Keystone et al,[6] 2004	1 Seminoma	Adalimumab, 20 mg weekly	8	1 Basal cell carcinoma	24
	1 Basal cell carcinoma†	Adalimumab, 20 mg weekly	8		
	1 GI adenocarcinoma	Adalimumab, 40 mg every other wk	14		
	1 Lymphoma (mixed B cell)	Adalimumab, 20 mg weekly	21		
	1 Basal cell carcinoma†	Adalimumab, 40 mg every other wk	22		
	1 Basal cell carcinoma†	Adalimumab, 40 mg every other wk	27		
	1 Squamous cell carcinoma†	Adalimumab, 40 mg every other wk	28		
	1 Breast cancer	Adalimumab, 40 mg every other wk	43		
	1 Lymphoma (B cell)†‡		67		
	1 Lymphoma (Hodgkin)†‡		88		
	1 Lymphoma (mixed B cell)†‡		114		
St Clair et al,[7] 2004	1 Leukemia	Infliximab, 6 mg every 4 wk	52	0	
	1 Endometrial cancer	Infliximab, 6 mg every 4 wk	3		
	1 Pancreatic cancer	Infliximab, 6 mg every 4 wk	15		
	1 GI adenocarcinoma	Infliximab, 6 mg every 4 wk	45		
Van de Putte et al,[33] 2004	1 Cholangiocarcinoma	Adalimumab, 40 mg every other wk	2	1 Basal cell carcinoma	6
	1 GI adenocarcinoma	Adalimumab, 40 mg weekly	9		
	1 Squamous cell carcinoma	Adalimumab, 40 mg every other wk	7		
	1 Basal cell carcinoma	Adalimumab, 20 mg every other wk	20		
	1 Lymphoma (mucosa-associated lymphoid tissue)†‡	NA	102		
Westhovens et al,[34] 2004	1 Lung cancer	Infliximab, 10 mg every 8 wk	6	1 Renal cell carcinoma	6
	1 Lung cancer	Infliximab, 10 mg every 8 wk	6		
	1 Lymphoma	Infliximab, 3 mg every 8 wk	7		

Abbreviations: GI, gastrointestinal tract; NA, data not available; TNF, tumor necrosis factor.
*Among participants who received at least 1 dose of the study drug.
†Not reported in original publication; on file with US Food and Drug Administration (http://www.fda.gov/_Hlt94332169o_Hlt94332169hrms/dockets/ac/03/briefing/3930B1_01_C--_Hlt103512168_Hlt103512168HUMIRA.Med.Review.pdf).
‡During follow-up, after actual trial period; not included in the meta-analysis.

Serious Infections

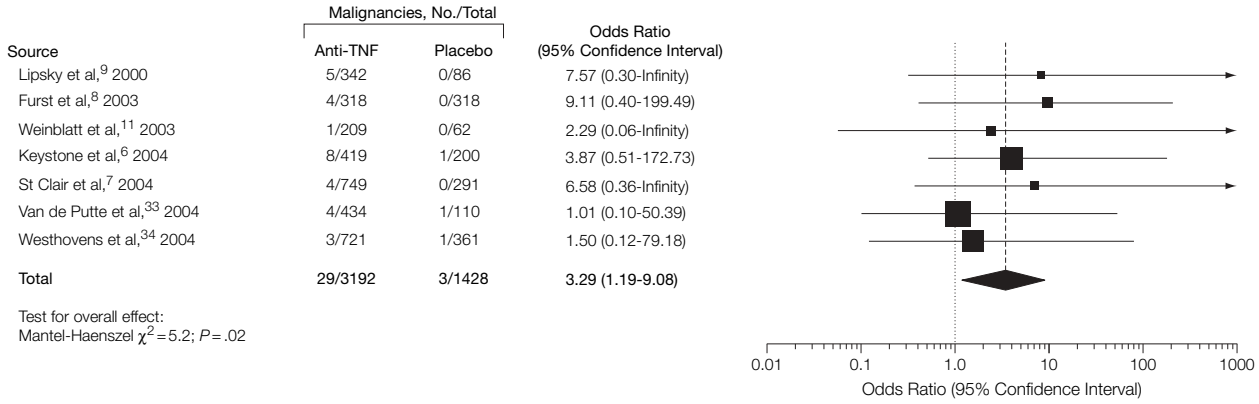
Serious infections were reported in 126 patients in the treatment groups and 26 patients in the control groups. Published data and FDA data differed in only 2 unreported cases, both of which were included for analysis after verification with the sponsors (TABLE 3).

Statistical heterogeneity was low (I^2=24%; 95% CI, 0%-66%) and not beyond variations that could be due to chance (P=.24).

The risk of serious infections in patients with RA treated with anti-TNF antibodies was increased compared with placebo patients (OR, 2.0; 95% CI, 1.3-3.1) (FIGURE 3). Estimates remained statistically significant when applying the Mantel-Haenszel methods without a continuity correction (OR, 2.0; 95% CI, 1.3-3.2), the Bayesian fixed-effects model (OR, 2.0; 95% CI, 1.3-3.3), and the conditional maximum likelihood approach (OR, 2.0; 95% CI, 1.3-3.3). The Bayesian random-effects analysis yielded an OR of 2.74 (95% CI, 1.07-26.36).

Stratified analysis according to anti-TNF antibody dose yielded a pooled OR of 2.3 (95% CI, 1.5-3.6) for the comparison of high-dose group vs placebo and an OR of 1.8 (95% CI, 1.1-3.1) for the comparison of low-dose group vs placebo. However, the OR of 1.4 (95% CI, 1.0-2.0) for the comparison of high-dose group vs low-dose group was not statistically significant (P=.07) (TABLE 4).

Figure 2. Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Malignancies in Patients With Rheumatoid Arthritis



TNF indicates tumor necrosis factor. Size of the data markers is proportional to the statistical weight of the trial.

Table 3. Summary of Serious Infections in Randomized Controlled Trials

Source	Anti-TNF–Treated Patients With ≥1 Serious Infection by Dose Group (No. of Participants*) (n = 3493)	Controls With ≥1 Serious Infection (No. of Participants*) (n = 1512)
Maini et al,[32] 1998	1 Infliximab, 10 mg every 4 wk (29) 1 Infliximab, 1 mg every 4 wk (29)/infliximab, 3 mg every 4 wk (29)	0 (14)
Lipsky et al,[9] 2000	13 Infliximab, 10 mg every 8 wk (81)/infliximab, 10 mg every 4 wk (87) 8 Infliximab, 3 mg every 8 wk (88)/infliximab, 3 mg every 4 wk (86)	7 (86)
Furst et al,[8] 2003	4 Adalimumab, 40 mg every other wk (318)	6 (318)
Van de Putte et al,[10] 2003	4 Adalimumab, 80 mg weekly (72)/adalimumab 40 mg weekly (70) 0 Adalimumab, 20 mg weekly (72)	0 (70)
Weinblatt et al,[11] 2003	3 Adalimumab, 40 mg every other wk (67)/adalimumab, 80 mg every other wk (73) 0 Adalimumab, 20 mg every other wk (69)	0 (62)
Keystone et al,[6] 2004	11 Adalimumab, 40 mg every other wk (207) 5 Adalimumab, 20 mg weekly (212)	1 (200)
St Clair et al,[7] 2004	19 Infliximab, 6 mg every 8 wk (377) 21 Infliximab, 3 mg every 8 wk (372)	6 (291)
Van de Putte et al,[33] 2004	3 Adalimumab, 40 mg every other wk (113)/adalimumab, 40 mg weekly (103) 8† Adalimumab, 20 mg every other wk (106)/adalimumab, 20 mg weekly (112)	0 (110)
Westhovens et al,[34] 2004	19 Infliximab, 10 mg every 8 wk (361) 6 Infliximab, 3 mg every 8 wk (360)	6 (361)

Abbreviation: TNF, tumor necrosis factor.
*Numbers of participants who received at least 1 dose of the study drug are shown in parentheses.
†One patient not reported in the original publication; information provided by the sponsor (Abbott).

Estimates of Absolute Risk

Since pooled ORs for malignancies and serious infections exceeded 1.5, we calculated the number needed to harm for both adverse events: For patients treated with anti-TNF antibodies in the included trials, the number needed to harm was 154 (95% CI, 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (95% CI, 39-125) within a treatment period of 3 to 12 months.

COMMENT

Our systematic review of randomized trials suggests an increased risk of malignancies and serious infections in patients with RA treated with anti-TNF antibod therapy. This association appears to be dose-dependent for malignancies and is derived from high-quality randomized trials. Because all necessary information to assess study quality, as well as the number of serious infections and malignancies, was verified and/or supplemented with detailed information provided by the pertinent FDA database, the principal investigators, and sponsors of the included trials (Abbott and Centocor), we regard the basis of our analysis in terms of completeness of data as very solid.

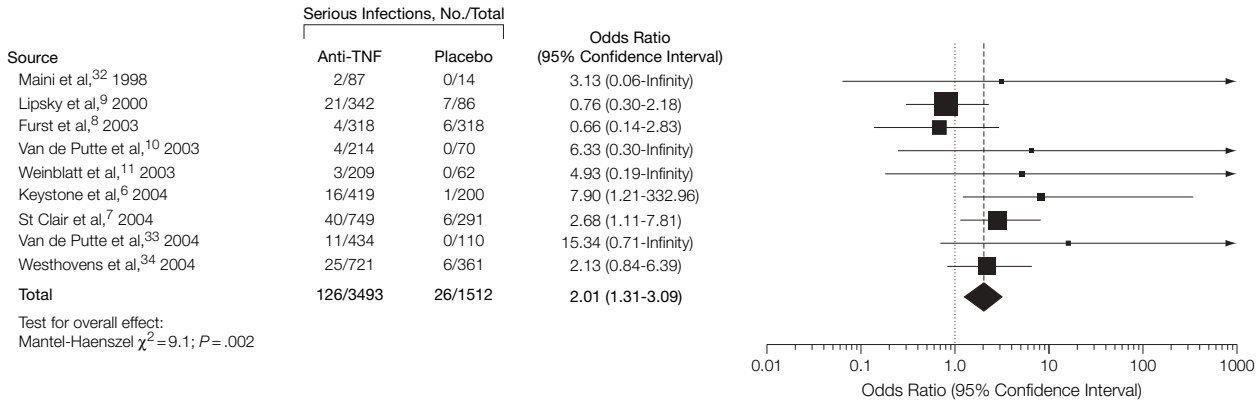
Limitations and Strengths

Readers should be aware of some important limitations of our study. Beyond statistical issues of handling sparse event data, simple mathematical instability is an inherent feature of calculations based on few events. Small changes in the numerator can result in major changes in the estimated risk and, therefore, in the risk comparisons across treatment groups. Furthermore, few events resulted in pooled estimates with limited precision (ie, wide CIs).

Included trials were clinically heterogeneous in terms of disease duration, disease activity, and previous/concomitant DMARD treatment. Therefore, inferences from our estimates of harm (which are derived from a mixed population of patients with RA) about certain patient subsets should be made with caution.[35] In addition, estimates were derived from trials lasting between 3 months and 1 year, and numbers may change significantly over time because constancy of effect should not be assumed for both events.

Conversely, the broadened range of patient characteristics in our analysis compared with patient populations in single randomized controlled trials strengthens the generalizability of our results.

Figure 3. Effect of Anti-TNF Antibody Therapy vs Control Therapy on Occurrence of 1 or More Serious Infections in Patients With Rheumatoid Arthritis



TNF indicates tumor necrosis factor. Size of the data markers is proportional to the statistical weight of the trial.

Table 4. Effect of Anti-TNF Antibody on Occurrence of 1 or More Malignancies or Serious Infections in Patients With Rheumatoid Arthritis, Stratified by Dose Group

	Odds Ratio (95% Confidence Interval)*			
Adverse Event	All Doses of Anti-TNF Antibody Therapy vs Placebo	Low-Dose Anti-TNF Antibody Therapy vs Placebo†	High-Dose Anti-TNF Antibody Therapy vs Placebo‡	High-Dose‡ vs Low-Dose† Anti-TNF Antibody Therapy
≥1 Malignancy	3.3 (1.2-9.1)	1.4 (0.3-5.7)	4.3 (1.6-11.8)	3.4 (1.4-8.2)
≥1 Serious infection	2.0 (1.3-3.1)	1.8 (1.1-3.1)	2.3 (1.5-3.6)	1.4 (1.0-2.0)

Abbreviation: TNF, tumor necrosis factor.
*Pooled odds ratio based on a fixed-effects Mantel-Haenszel model for the all-doses estimate and based on high-dose/low-dose stratification.
†Infliximab, ≤3 mg/kg every 4 weeks, or adalimumab, 20 mg/wk.
‡Infliximab, ≥6 mg/kg every 8 weeks, or adalimumab, 40 mg every other week.

Potentially confounding variables such as age, disease duration, and disease activity were equally distributed between treatment and control groups, and confounding by indication was effectively eliminated in this analysis because all patients were subject to random allocation.

We preferred to use the number of randomized patients, rather than patient years of drug exposure, as the denominator of our incidence measure. The latter would not only require individual patient data (which is not provided in the original articles) but also entails several pitfalls by assuming a linear and proportional occurrence of events and erroneously equating the risk of harm over time with the risk of harm over the number exposed, a problematic approach in a setting where an adverse event such as a malignancy takes time to become clinically detectable.

Of the 9 trials included in our analysis, 4 showed a higher dropout rate among placebo study participants compared with anti-TNF–treated patients. As a consequence, some anti-TNF–treated patients had a longer exposure to the concomitant DMARD therapy (methotrexate) than patients with additional placebo. This leads to the theoretical danger that the higher number of adverse events in the anti-TNF–treated individuals is due to the longer duration of concomitant methotrexate exposure during the trial. However, no studies have shown so far that methotrexate increases the overall risk of malignancies in patients with RA,[36] and a recent population-based trial[16] demonstrated a similar incidence of infections in patients with RA treated with methotrexate and without.

Furthermore, the 4 trials that showed imbalances in the percentage of withdrawals between treatment and control groups had only 66 patients overall who were exposed to methotrexate for a shorter time in the control groups compared with the anti-TNF–treated groups. It appears highly unlikely that our estimates are distorted by this degree of imbalance in exposure to the baseline drug during the trial.

Serious Infections

Our findings of a significant increase in serious infections in patients treated with TNF antagonists is consistent with current knowledge of the biological actions of TNF and its role combating infections[2-4] and with findings of large observational studies and randomized controlled trials including larger samples.[6,7,12-14]

Our results are further supported by the recently published report from the German Biologics Register,[37] which showed a relative risk of 3.0 (95% CI, 1.8-5.1) for serious infections in patients treated with the anti-TNF antibody infliximab after adjusting for other predictive factors of infection risk, including patient age and disease severity. Finally, 3 of the 4 randomized controlled trials that randomized more than 600 patients to anti-TNF antibody treatment vs placebo[6-8] and Westhovens et al[34] have shown a statistically significant increase of serious infections in at least 1 active treatment arm.

The association of anti-TNF therapy and serious infections has generally been attributed to an increased risk of granulomatous infections. However, only 12 of the 126 serious infections reported in the included randomized controlled trials could be identified as granulomatous (10 cases of tuberculosis, 1 case of histoplasmosis, and 1 case of coccidiomycosis). Exclusion of these infections from our analysis still yielded an elevated OR for infection of 1.9 (95% CI, 1.2-2.9).

Malignancies

Malignancies in single randomized trials of anti-TNF antibody therapy for RA were rare and observed differences in their occurrence between groups were not statistically significant. However, a recently published trial in patients with Wegener granulomatosis revealed a statistically significant increase in the incidence of solid malignancies in patients treated with the TNF fusion protein etanercept (6 solid cancers in 89 patients treated with etanercept plus cyclophosphamide vs no malignancy in 91 control patients treated with cyclophosphamide alone).[38] In addition, a large cohort study demonstrated an increased risk of nonmelanoma skin cancers in patients with RA treated with anti-TNF agents in combination with methotrexate, even after adjustment for important covariates.[39] Nonhematological malignancies did not seem to occur with an increased frequency when comparing the incidence rate in randomized controlled trials with population-based incidence data.[6,7,9,33] However, this approach carries several pitfalls. Beyond the limited statistical power and the difficulties in correcting for additional risk factors such as age, sex, race/ethnicity, length of follow-up, multiple events, and nonlinear relationship between exposure and event, selection and detection bias are a major concern when comparing population-based data with results derived from randomized controlled trials. Patients participating in clinical trials usually enter the study through a tight filter of regular visits, multiple exclusion criteria, physical examinations, radiographic studies, blood tests, easy access to preventive measures, and so on. Imputing the risk of developing a clinically detectable malignancy in the following 6 to 12 months of observation by taking the number of events in the general population might lead to incorrect estimates.

Our findings are somewhat inconsistent with the results of a Swedish study that did not show a significantly increased incidence of solid malignancies when comparing a large cohort of anti-TNF–treated patients with the general population.[40] However, the number of expected events in patients with RA receiving anti-TNF therapy was imputed from other data sources. In contrast to a randomized control group such as in our analysis, there might be substantial differences in various risk factors between anti-TNF–treated patients and the population-based comparison group. Since our dose-effect analysis demonstrated a more prominent risk for patients who received higher doses of anti-TNF antibody therapy, the discrepancy could also be

well explained by a lower number of patients receiving higher doses of anti-TNF antibodies in the Swedish cohort. It remains unclear whether a risk estimate derived from the general population is a good imputation for patients with RA selected for anti-TNF therapy.

Focus on Anti-TNF Antibodies

We excluded the anti-TNF agent etanercept from our analysis. Although the currently licensed anti-TNF agents infliximab, adalimumab, and etanercept are all potent inhibitors of TNF bioactivity, there are fundamental differences in their molecular structures, their binding specificities, and their effect on proinflammatory cytokine release and lymphocyte apoptosis.

Infliximab and adalimumab are both anti-TNF antibodies not known to bind to any antigen other than TNF, while etanercept is a fusion protein made up of the extracellular domain of the p75 TNF receptor, binding equally well to both TNF and lymphotoxin-α.[41] Lymphotoxin-α is a cytokine that is considered to have an important role in infection and tumor growth control independent of TNF activity.[42-46]

Anti-TNF antibodies and etanercept are both capable of inducing apoptosis in synovial macrophages.[47] But unlike etanercept, anti-TNF antibodies also induce apoptosis in highly activated lymphocytes from patients with Crohn disease.[48] In addition, the antibodies have a more potent effect on lipoprotein serine–induced cytokine release in macrophages compared with etanercept.[49]

Consistent with this experimental data on differences between the anti-TNF antibodies and etanercept, clinical trials in Crohn disease and other granulomatous diseases indicated a distinct difference in clinical effectiveness of the 2 agent groups, although they have similar clinical benefit in RA.[50] There are also important distinctions in the safety profiles between the groups, most notably an increased risk of intracellular infections rather specific to the TNF agent used[51] and a possible increased risk of certain neurological disorders in patients taking etanercept.[52]

The heterogeneous modulation of different immune pathways and the differences in clinical trials and safety assessments formed the rationale for not including etanercept in this meta-analysis, to avoid the danger of overestimating or underestimating an adverse effect that involves physiologic mechanisms differentially affected by the 2 principal modes of TNF blockade represented by these agents.

Statistical Approach

Our meta-analysis was based on a method that has been thoroughly evaluated for the analysis of sparse event data in the presence of imbalanced groups.[19] For the first time, we used this validated technique as a tool for the evaluation of drug safety. Sensitivity analysis including a variety of other statistical models suggested for analysis of sparse event data gave very similar estimates, which all remained statistically significant.

Clinical Significance of the Analysis

The striking effectiveness of TNF inhibition redefined therapy for RA, most notably because of the ability of these agents to improve measures of disease activity and prevent a disabling disease course in patients who fail to respond to conventional DMARD treatment. At the same time, our analysis contributes to the findings that challenge the previously presumed safety profile of anti-TNF therapy. The detected increase of 2 serious adverse events has to be interpreted in the light of the high effectiveness of anti-TNF therapy in patients with RA and the lack of therapeutic alternatives in cases with high disease activity irresponsive to traditional DMARD therapy. The reduction of joint destruction, gain in mobility, and increase in quality of life, even in patients with RA who poor response to treatment prior to the introduction of anti-TNF therapy, must be taken into account when considering therapeutic risks and benefits in individual patients. The potent anti-inflammatory effects of anti-TNF agents may have a significant positive impact on the overall survival of patients with RA if they reduce disease activity and result in a lessening of cardiovascular events, which are the main cause of death in patients with RA.[53,54]

Our systematic review did not show an accumulation of malignancies with longer study duration. This could be explained by an acceleration of preexisting subclinical malignancies rather than induction, which should result in clustering of events with prolonged exposure to the study drug. Accordingly, thorough screening for subclinical malignancies of patients being considered for anti-TNF antibody treatment and subsequent surveillance may represent a strategy to improve the safety of anti-TNF therapy that deserves further evaluation.

Our findings of a dose-dependent increase in the risk of malignancies should also be taken into account when considering anti-TNF antibody treatment in patients with RA. Pharmacokinetic studies have already shown that infliximab doses beyond 3 mg/kg every 8 weeks lead to a high risk of overexposure with an excessive binding of TNF.[55] The differences in terms of clinical efficacy between low-dose anti-TNF antibody treatment (adalimumab, 20 mg every other week, or infliximab, 1 mg/kg every 4 weeks) and the currently recommended substantially higher doses were marginal and statistically not significant in published clinical trials.[10,11,33,56] If a very small (or *any*) gain in primary efficacy appears to come at the cost of a significant increase in serious adverse events, initial application of doses that are lower than those currently licensed might result in an improved risk-benefit ratio. Also, the use of anti-TNF antibodies only as induction therapy might have potential[57] and should be further evaluated.

In general, the formal meta-analysis of premarketing data appears to offer a powerful tool for early detection of drug hazards, preventing an unneces-

sary delay in detection of potential safety problems in the course of pharmacovigilance. As recently suggested, preplanned meta-analysis as part of the regulatory process could help to minimize different sources of bias associated with a post hoc analysis and obtain a more generalizable estimate of harmful drug effects.[58]

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Author Contributions: Drs Bongartz and Matteson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bongartz, Matteson, Montori, Sutton, Sweeting, Buchan.

Acquisition of data: Bongartz, Matteson.

Analysis and interpretation of data: Bongartz, Matteson, Montori, Sutton, Sweeting, Buchan.

Drafting of the manuscript: Bongartz, Matteson, Montori.

Critical revision of the manuscript for important intellectual content: Bongartz, Matteson, Montori, Sutton, Sweeting, Buchan.

Statistical analysis: Sutton, Sweeting, Buchan.

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In a very real sense, people who have read good literature have lived more than people who cannot or will not read. . . . It is not true that we have only one life to live; if we can read, we can live as many more lives and as many kinds of lives as we wish.
—S. I. Hayakawa (1906-1992)

CORRECTION

Incorrect Statements on Funding/Support and Role of the Sponsors and Incorrect and Incomplete Financial Disclosures: In the Review entitled "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" published in the May 17, 2006, issue of *JAMA* (2006; 295:2275-2285), the following errors appeared:

After this issue was printed and mailed, *JAMA* was informed by the authors that information reported on page 2284 of the article was incorrect.

The Funding/Support statement should have read "This study was supported by the Mayo Foundation. Additional data were provided by Abbott and Centocor. Data provided by Abbott were subject to a confidentiality agreement."

The Role of the Sponsors statement should have read "Abbott and Centocor did not have any role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation or approval of the manuscript. The manuscript was sent to Abbott for review prior to submission for publication."

The Financial Disclosures statement should have read: "Dr Bongartz reported that he has given lectures for Abbott as part of seminars for study nurses and received honorarium in the form of a medical textbook for the Internal Medicine library; he received an educational grant from Amgen in February 2006 to perform the same type of analysis of harmful events under anti-TNF treatment for etanercept; and he received the 2005 Fellow's Award of the American College of Rheumatology, which was supported by Amgen.

Dr Matteson reported that he has been a paid consultant for Centocor for work unrelated to this study and has been working with Wyeth and Amgen to perform a similar analysis for etanercept; he has been an Investigator for the American College of Rheumatology, Amgen, Asta, Biogen-IDEC, Burroughs-Wellcome, Centocor, Cypress, Endocyte Inc, Genentech, Hoffmann-LaRoche, Human Genome Sciences, Immunex, Protein Design Laboratories, Nastech, Pharmacia & Upjohn, Schering, Wyeth, and Xoma Corp; he has received grant support from Amgen, Aventis, Centocor/Johnson & Johnson, Genentech, Immunex, Mayo Foundation, Novartis, and the National Institutes of Health; and he has been a consultant for Amgen, BoneandJoint.org, Burroughs-Wellcome, Centocor, Regeneron, Takeda, Upjohn, Watermark Research, and the Vasculitis Foundation."

This correction is being published online on May 16, 2006. Because of the nature and extensiveness of this incorrect and incomplete reporting, *JAMA* has requested that the Mayo Clinic College of Medicine conduct an investigation. *JAMA* will publish another correction or clarification once the results of that investigation become available.

Table. Annual Number of Laparoscopic Cases

Procedure	Years Since Introduction														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Cholecystectomy	16 247	93 464	270 991	363 161	354 565	348 323	331 076	333 600	327 092	316 733	319 793	346 157	351 736	360 844	358 069
Fundoplication	19	184	1613	5299	11 245	13 111	15 802	18 399	23 993	24 761	24 188	18 981	19 042		
Hysterectomy	4838	6181	13 102	38 929	44 852	41 401	42 335	48 578	68 455	60 805	60 733	64 639	69 659	71 977	76 033
Nephrectomy indication															
Cancer	35	236	215	199	283	308	563	532	701	1226	1968	4221	5093		
Benign disease	452	454	573	614	767	898	1261	1055	1947	1662	1896	2823	3388		
Donor	11	4	19	21	40	154	473	449	510	1589	1305	1648	1789		

Critical revision of the manuscript for important intellectual content: Miller, Dunn, Wei, Hollenbeck.
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Role of the Sponsor: The study sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

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CORRECTIONS

Incorrect Unit of Measure: In the Original Contribution entitled "Effect of 6-Month Calorie Restriction on Biomarkers of Longevity, Metabolic Adaptation, and Oxidative Stress in Overweight Individuals: A Randomized Controlled Trial" published in the April 5, 2006, issue of *JAMA* (2006;295:1539-1548), an incorrect unit of measure was given for dehydroepiandrosterone sulfate (DHEAS). On page 1543 (Table 1) and page 1544 (Figure 3), the unit of measure for DHEAS should be µg/dL (not ng/mL).

Error in Byline: In the Original Contribution entitled "Incidence and Prognostic Implications of Stable Angina Pectoris Among Women and Men" published in the March 22/29, 2006, issue of *JAMA* (2006;295:1404-1411), the byline contained an incorrect academic degree. Alison McCallum should have been listed as having an MBChB, FFPH.

Incorrect Data: In the Original Contribution entitled "Frequency and Effect of Adjuvant Radiation Therapy Among Women With Stage I Endometrial Adenocarcinoma" published in the January 25, 2006, issue of *JAMA* (2006;295:389-397), incorrect data were reported in the "Results" section of the article. On page 391, the sentence "Within the RT cohort, 2551 patients (62.5%) had external beam radiation, 732 (17.9%) had vaginal brachytherapy, and 1078 (26.4%) received a combination of external beam radiation with vaginal brachytherapy" should have read "Within the RT cohort, 2378 patients (58.3%) received external beam radiation, 962 (23.6%) received external beam and brachytherapy radiation, 654 (16.0%) received brachytherapy radiation alone, and for 86 (2.1%) the radiation modality was not specified." The authors verified that this error did not have an impact on the data set or subsequent statistical analyses.

Incorrect Statements on Funding/Support and Role of the Sponsors and Incorrect and Incomplete Financial Disclosures: In the Review entitled "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" published in the May 17, 2006, issue of *JAMA* (2006;295:2275-2285), the following errors appeared:

After this issue was printed and mailed, *JAMA* was informed by the authors that information reported on page 2284 of the article was incorrect.

The Funding/Support statement should have read "This study was supported by the Mayo Foundation. Additional data were provided by Abbott and Centocor. Data provided by Abbott were subject to a confidentiality agreement."

The Role of the Sponsors statement should have read "Abbott and Centocor did not have any role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation or approval of the manuscript. The manuscript was sent to Abbott for review prior to submission for publication."

The Financial Disclosures statement should have read: "Dr Bongartz reported that he has given lectures for Abbott as part of seminars for study nurses and received honorarium in the form of a medical textbook for the Internal Medicine library; he received an educational grant from Amgen in February 2006 to perform the same type of analysis of harmful events under anti-TNF treatment for etanercept; and he received the 2005 Fellow's Award of the American College of Rheumatology, which was supported by Amgen."

Dr Matteson reported that he has been a paid consultant for Centocor for work unrelated to this study and has been working with Wyeth and Amgen to perform a similar analysis for etanercept; he has been an Investigator for the American College of Rheumatology, Amgen, Asta, Biogen-IDEC, Burroughs-Wellcome, Centocor, Cypress, Endocyte Inc, Genentech, Hoffmann-LaRoche, Human Genome Sciences, Immunex, Protein Design Laboratories, Nastech, Pharmacia & Upjohn, Schering, Wyeth, and Xoma Corp; he has received grant support from Amgen, Aventis, Centocor/Johnson & Johnson, Genentech, Immunex, Mayo Foundation, Novartis, and the National Institutes of Health; and he has been a consultant for Amgen, BoneandJoint.org, Burroughs-Wellcome, Centocor, Regeneron, Takeda, Upjohn, Watermark Research, and the Vasculitis Foundation."

This correction was published online on May 16, 2006. Because of the nature and extensiveness of this incorrect and incomplete reporting, *JAMA* has requested that the Mayo Clinic College of Medicine conduct an investigation. *JAMA* will publish another correction or clarification once the results of that investigation become available.