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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CRD summary
This well-conducted review evaluated the relationship between anti-tumour necrosis factor (TNF) antibody treatment and the incidence of malignancies and serious infections. The authors concluded that anti-TNF antibody therapy significantly increases the incidence of both outcomes compared with placebo, and that the relationship between treatment and incidence of malignancy is dose-dependent. These conclusions are likely to be reliable.

Authors' objectives
To determine whether anti-tumour necrosis factor (TNF) antibody therapy increases the risk of serious infections and malignancies in patients with rheumatoid arthritis.

Searching
MEDLINE, EMBASE and the Cochrane Library were searched from inception to December 2005; the search terms were reported. In addition, the abstract databases of the European League Against Rheumatism and the American College of Rheumatology were searched from 1996 onwards to locate unpublished trials. The manufacturers of both included anti-TNF antibody treatments were also contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
The anti-TNF antibody treatments infliximab and adalimumab were eligible for inclusion in the review. Trials that were placebo-controlled were also eligible, as were trials in which patients were given traditional disease-modifying antirheumatic drugs in addition to anti-TNF antibody or placebo treatment. The anti-TNF agent etanercept was excluded from the review.

Participants included in the review
Trials including patients with rheumatoid arthritis, classified according to the criteria of the American College of Rheumatology, were eligible for inclusion. The patients included in the review were predominantly those with high disease activity despite treatment with traditional disease-modifying antirheumatic drugs, but patients with early disease, high disease activity and disease duration of less than 3 years were also included.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not stated. The outcomes included in the review were serious infection and malignancy. Serious infection was defined as that requiring antimicrobial treatment or hospitalisation.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion in the review. Any disagreements were resolved through consensus.

Assessment of study quality
The studies were assessed for validity using the following criteria: randomisation, allocation concealment, masking of allocation, intention-to-treat analysis, completeness of follow-up, outcome assessment and attrition. Two reviewers
independently assessed the studies for validity.

Data extraction
Two reviewers independently extracted the data for the review. Data on serious infections and malignancies were extracted from published reports. These data were verified by checking the database of the U.S. Food and Drug Administration. In addition, authors and sponsors were contacted to further verify data and to provide additional information on the type and time of occurrence of malignancies. Odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated for each outcome.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis using a fixed-effect model (Mantel-Haenszel) with a Robins-Breslow-Greenland variance to calculate pooled ORs for each outcome. A continuity correction for sparse data was employed. In cases where a pooled OR was 1.5 or greater, the number-needed-to-harm was calculated. Statistical sensitivity analyses were also conducted to explore the impact of the following: conducting the meta-analysis without a continuity correction; employing Bayesian fixed-effect and random-effects models; and employing a conditional maximum likelihood approach.

How were differences between studies investigated?
Statistical heterogeneity between trials was assessed using the I-squared statistic. In assessing malignancies, sensitivity analyses were conducted that excluded trials for the following reasons: omission of malignancies diagnosed within the first 6 weeks of a trial; and omission of malignancies classified as nonmelanoma skin cancer. Analyses that excluded trials which reported no events for the analysis were also conducted. An a priori subgroup analysis of trials using high- and low-dose anti-TNF treatment was also conducted.

Results of the review
Nine RCTs with 5,014 patients were included in the review.

All trials contained potential risks to treatment allocation concealment because of the occurrence of adverse reactions in the treatment arms. Only two trials reported losses to follow-up.

Malignancies.
There was a significantly higher incidence of malignancies in patients in the anti-TNF antibody groups than in the placebo groups. The pooled OR for all trials which reported at least one event in any group was 3.3 (95% CI: 1.2, 9.1). This finding remained significant for all the alternative analyses employed. There was no statistically significant heterogeneity between the trials (I-squared 0%, 95% CI: 0, 25). The number-needed-to-harm was calculated to be 154 (95% CI: 91, 500) in a treatment period of 6 to 12 months.

A sensitivity analysis that omitted trials which disregarded malignancies diagnosed within the first 6 weeks of a trial also found a significantly increased incidence in anti-TNF groups (OR 4.5, 95% CI: 1.3, 15.8), as did an analysis that omitted trials which disregarded nonmelanoma skin cancers (OR 3.7, 95% CI: 1.0, 13.2).

Subgroup analyses found that the effect of anti-TNF antibodies on malignancy incidence was higher in trials using higher doses of the drugs. The pooled OR was 4.3 (95% CI: 1.6, 11.8) for trials using a high dose of anti-TNF antibodies and 1.4 (95% CI: 0.3, 5.7) for trials using a low dose. A direct comparison of high- versus low-dose anti-TNF antibodies produced an OR of 3.4 (95% CI: 1.4, 8.2), indicating that the incidence of malignancy was statistically significantly higher in the groups given higher doses of the antibodies.

Serious infections.
There was a significantly higher incidence of serious infections in patients in the anti-TNF antibody groups than in the placebo groups. The pooled OR for all trials which reported at least one event in any group was 2.0 (95% CI: 1.3, 3.1).
This finding remained significant for all the alternative analyses employed, with the exception of the Bayesian random-effects analysis. There was no statistically significant heterogeneity between the trials (I-squared 24%, 95% CI: 0, 66, P=0.24). The number-needed-to-harm was calculated to be 59 (95% CI: 39, 125) in a treatment period of 3 to 12 months.

Subgroup analyses did not find an effect of anti-TNF antibody dose on the incidence of serious infections. The pooled OR was 2.3 (95% CI: 1.5, 3.6) for trials using a high dose of anti-TNF antibodies and still statistically significant (OR 1.8, 95% CI: 1.1, 3.1) for trials using a low dose. A direct comparison of high- versus low-dose anti-TNF antibodies did not find a statistically significant difference between the groups (OR 1.4, 95% CI: 1.0, 2.0).

Authors’ conclusions
There is evidence of an increased risk of both serious infections and malignancies in patients with rheumatoid arthritis treated with anti-TNF antibody therapy. This effect was dose-dependent in the case of malignancies.

CRD commentary
The review question was clear and, with the exception of outcomes, inclusion criteria were defined. The authors searched several relevant databases and took steps to locate unpublished trials. They also employed rigorous methods to minimise bias and error at the study selection, validity assessment and data extraction stages of the review. Appropriate criteria were used to assess study validity, although this assessment did not contribute to the analysis. The meta-analysis and subgroup analyses used techniques appropriate for the data, and substantial efforts were made to ensure that the choice of analysis did not disproportionately influence the results. This was a generally well-conducted review and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors appeared to state that the risks of anti-TNF antibody therapy should be considered in conjunction with its considerable efficacy, but that lower doses should be considered in light of the dose-dependent effect on incidence of malignancies.

Research: The authors stated that the use of anti-TNF antibody therapy should be evaluated only as induction therapy.

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Other publications of related interest
This additional published commentary may also be of interest. Shoor S. Review: anti-tumour necrosis factor antibody therapy for rheumatoid arthritis increases risk for serious infection and malignancy. ACP J Club 2006;145:65.
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract
contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on
the reliability of the review and the conclusions drawn.